CLINICAL STUDY PROTOCOL

Prostaglandin insert (Propess) versus trans-cervical balloon catheter for out-patient labour induction: A randomised controlled trial of feasibility (PROBIT-F)

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Funding source: National Institute of Health Research (Research for patient benefit stream) will fund the study.

Signature Page and Statement

The Chief Investigator (CI) and the Sponsor representative have discussed this protocol version. The investigators agree to perform the investigations and to abide by this protocol except in the case of medical emergency (Section 12.6) or where departures from the protocol are mutually agreed in writing.

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP and UK Regulations for CTIMPs (SI 2004/1031; as amended), the UK Data Protection Act (2018), the St George's NHS Trust Information Governance Policy (or other local equivalent), the UK Policy Framework for Health and Social Care Research (V3.2 October 2017), the Sponsor's SOPs, and other regulatory requirements as amended.

This protocol has been written in accordance to the Sponsor's procedure identified as: JREOSOP0039 'Protocol Design' and is intended for use at UK sites only.

Chief Investigator Dr. Amarnath Bhide Consultant Obstetrician St George's University Hospitals NHS Foundation Trust	Signature	Date
Sponsor Representative Subhir Bedi St George's University Hospitals NHS Foundation Trust		

Acknowledgements and Protocol contributories

Amarnath Bhide (St. George's Hospital) conceived the study; Amar Bhide, Philip Sedgwick, Christine McCourt, initiated the study design. Sandra Linton, Barbara Barrett & Debs Rolfe helped with implementation. AB, PS, CM, SL BB and Rosie Goode are grant holders, Philip Sedgwick provided statistical expertise in clinical trial design and is conducting primary statistical analysis. All authors contributed to refinement of the study protocol and approved the final manuscript.

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Contents

1. List of abbreviations 5
2. Roles and Responsibilities 6
3. Study synopsis 8
4. Primary Objective 10
5. Secondary Objectives 10
6. Background 10
Study Rationale and risk/benefit analysis 12
Assessment & management of potential risk 12
7. Trial design 12
7.1 Overall design 12
8. IMP Dosage regimen and rationale 12
8.1 IMPs and non-IMPs used in the trial 12
8.2 Source of IMP 13
8.3 Accountability procedures for the IMP(s) 13
8.4 Assessment of compliance 13
8.5 Name and description of each non-IMP (NIMP) 13
8.6 Concomitant treatment 13
8.7 Interventions involving a device 13
9. Participant Selection criteria 14
Inclusion criteria 14
Exclusion criteria 14
9 Subject/Patient Recruitment process 15
10 Study procedures 15
10.1 Informed consent 15
10.2 Randomisation procedure 16
10.3 Prescribing & Dispensing of IMP /Device 18
10.4 Discontinuation/withdrawal of participants and stopping rules 18
10.5 Participant transfers 19
10.6 Lost to Follow up 19
10.7 Definition of the End of Trial 19
11 Study Assessments 19
11.1 Screening assessments 19
11.2 Baseline assessments 19
11.3 Intervention 20
12 Safety and Pharmacovigilance 23
12.1 Definitions 23
12.2 Investigator responsibilities relating to safety reporting 24
12.3 Notification of deaths 26
12.4 Development Safety Update Reports (DSURs) 26
12.5 Annual Progress Reports (APRs) 26
12.6 Reporting Urgent Safety Measures 26
12.7 Notification of Serious Breaches of GCP and/or the protocol 26

13 Data management and quality assurance 27
13.1 Confidentiality 27
13.2 Data collection tool 27
13.3 Data handling and analysis 27
14 Archiving arrangements 27
15 Statistical design 28
15.1 Statistical input in trial design 28
15.2 Endpoints 28
15.2.1 Primary endpoint 28
15.3 Sample size and recruitment 28
15.3.1 Sample size calculation 28
15.3.2 Planned recruitment rate 28
15.4 Statistical analysis plan 29
15.4.1 Summary of baseline data and flow of patients 29
15.5 Randomisation 29
15.6 Interim analysis 29
15.7 Other statistical considerations 29
16 Direct access to source data 29
17 Site approval and ongoing Regulatory compliance 30
18 Monitoring plan for the trial 30
19 Finance 31
20 Insurance and indemnity 31
21 IP and development policy 31
22 Publication policy 31
22.1 Before the official completion of the Trial 32
22.2 Up to 180 days after the official completion of the Trial 32
22.3 Beyond 180 days after the official completion of the Trial 32
23 Statement of compliance 33
24 List of Protocol appendices 33
25 References 33

1. List of abbreviations

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTG	Cardiotocograph
CTU	Clinical Trials Unit
CTIMP	Clinical Trial of Investigational Medicinal Product
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IoL	Induction of Labour
ISF	Investigator Site File
ITT	Intention to treat
JREO	Joint Research & Enterprise Office
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
NHS R&D	National Health Service Research & Development
NIMP	Non- Investigational Medicinal Product
PI	Principal Investigator
PIS	Participant Information Sheet
RCT	Randomised Control Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

2. Roles and Responsibilities

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SAE REPORTING	**All events** Adverseevents@sgul.ac.uk **Tel :** 020 8725 5013 **Fax:** 020 8725 0794 **AND for** Device related events Cook Medical Europe Ltd Medical Safety Officer **Tel:** 00 353 61 334440 **Fax**: 00 353 61 334441 Refer to Protocol section **12.2** for instructions
Trial Management Group:	Dr Amar Bhide, Ms. Sandra Linton, Ms. Debbie Rolfe, Dr Sharon Griffin, Ms. Sue Cromarty.
Trial Steering Committee:	Independent Members Professor Lucy Chappell (Chair) Professor Andrew Weeks PPI – Rosie Goode Dr. Louise Marston (statistician) Non-Independent Members Dr Amar Bhide Observers Debbie Rolfe/Sue Cromarty (Sponsor Delegate) Dr Phillip Sedgwick (Statistical expert) Dr Barbara Barrett- (Health economist, TBC)

3. Study synopsis

Brief Title	PROBIT - F
Official title:	Prostaglandin insert (Propess) versus trans-cervical balloon catheter for out-patient labour induction: A randomised controlled trial of feasibility (PROBIT-F)
Brief Summary	This study will randomise low-risk women to compare the effectiveness of trans-cervical balloon catheter for pre-induction cervical ripening for out-patient induction of labour with current practice (Propess). Women will be randomised to two treatment groups. We wish to explore if such a trial is feasible, acceptable to women and what data collection is required for a future trial. Since no data exist, we propose a study with approximately 60 women in each arm across two recruiting sites.
Sponsor reference number:	13.0029
Public database Trial identifier number	NCT03199820
EUdraCT no.	2017-001914-27
Study type & Phase	CTIMP/Device Phase IV
Study Design	Randomised Controlled Trial
Chief Investigator:	Dr. Amarnath Bhide Consultant Obstetrician St George's University Hospitals NHS Foundation Trust
Study Population	Low risk pregnant women requiring induction of labour
Condition	Pregnant women needing induction of labour
Study Group/cohort (s)	Randomised controlled trial to compare trans-cervical balloon catheter with Prostaglandins for out-patient induction of labour in low-risk women
Eligibility criteria:	***Inclusion criteria:*** 1 Pregnant women with a single fetus and uncomplicated pregnancy, with a gestational age > 37+ 0 weeks, needing induction of labour. 2. ≥ 18 years of age 3. No medical risk factors.
	Exclusion criteria: 1. Out-patient induction of labour is deemed unsuitable for the following women on the grounds of safety - a. Grand multiparous women (Parity 5 or more) b. Multiple pregnancy c. Women with complex medical or obstetric problems d. Previous caesarean section/uterine scar 2. Women who are contracting and/ or requiring analgesia 3. Women who do not fully understand the information leaflet and unable to provide full informed consent 4. Women for whom out-patient induction is unsuitable according to local hospital protocol

Target number of participants:	120 participants over two recruiting sites
Criteria for evaluation:	*Primary outcome measure(s):* The feasibility study will be deemed successful if • The expected number of women (120) are recruited and randomised for participation in to the trial in a 12-month recruitment period. • It is possible to collect data needed to assess if a full RCT is feasible for quantifying a reduction in unplanned admission after commencing out-patient induction of labour.
Sources of funding:	National Institute of Health Research (Research for patient benefit stream). PB-PG-0815-20022
Anticipated start date:	*September 1st, 2017*
Anticipated primary completion date:	*August 31st, 2018*
Sponsor	St George's University Hospitals NHS Foundation Trust
Contact names	*Sponsor representative:* Subhir Bedi JRES St George's University Hospitals NHS Foundation Trust *Chief Investigator :* Dr. Amarnath Bhide Consultant Obstetrician St George's University Hospitals NHS Foundation Trust

4. Primary Objective

Primary objective is to assess the feasibility of conducting a randomised controlled trial.

5. Secondary Objectives

- To assess the clinical efficacy, cost effectiveness and safety of trans-cervical balloon catheter compared to Prostaglandins (Propess) for out-patient induction of labour in low-risk women.
- To determine women's willingness to be randomised
- To determine the acceptability of using the balloon catheter
- To collect pilot data to plan an appropriately powered randomised controlled trial based on key clinical variables.
- To pilot data collection instruments for economic evaluation.
- To examine women's views on out-patient induction of labour (NICE, 2008)
- To assess women's experience with these methods and their preference.

6. Background

The rate of induction of labour in the UK has increased steadily over the last decade and approximately 20% of all pregnant women undergo labour induction. A Cochrane review has shown that mechanical methods (trans-cervical balloon catheter) of cervical ripening for induction of labour are as effective as vaginal prostaglandins (Jozwiac et al, 2012). Currently, women undergoing induction of labour are admitted to the hospital prior to the administration of prostaglandins. A Cochrane review assessing methods of outpatient labour induction concluded that induction of labour in outpatient settings was feasible. However, there is limited evidence as to which induction methods are preferred by women, or the interventions that are most effective and safe to use in outpatient settings. The UK Database of Uncertainties about the Effects of Treatments (UK DUETs) identifies mechanical methods of labour induction as a known uncertainty, and recommends that future studies on mechanical methods for induction of labour should be of large sample size and report on substantive outcomes. Hyper stimulation, including the effect on fetal well-being and maternal discomfort should be carefully assessed. An economic analysis comparing mechanical methods to prostaglandins for cervical ripening would be beneficial. In a recent randomised controlled trial (Henry, 2013), 101 women with an unfavourable cervix requiring induction of labour at term were randomised to outpatient care using Foley catheter or inpatient care using vaginal PGE_2. The authors reported that the out-patient group had shorter hospital stay prior to birth. Vaginal birth rates, total induction to delivery time and total inpatient times were similar. However, this study was performed in Australia, and did not address patient preference.

A recent trial showed that for women with an unfavourable cervix at term, success of induction of labour with a Foley catheter is similar to induction of labour with prostaglandin E2 gel, with fewer maternal and neonatal side-effects, but similar Caesarean section rates (Jozwiac, 2011). A previous study (Pennell et al, 2009) reported lower pain scores with the use of trans-cervical balloon catheter, as compared to vaginal PGE2 gel. Both these were apparently in in-patient setting. The OPRA study (Wilkinson et al, 2014) compared clinical outcomes from outpatient with inpatient cervical prostaglandin E2 ripening for low risk labour induction. They concluded that uterine stimulation following prostaglandins may preclude a woman from going home or remaining

at home overnight, and may not be the best agent for outpatient ripening. The sustained release vaginal prostaglandin (Propess) is our standard practice for induction of labour at St. George's Hospital, Tooting and Medway Hospitals, Kent. Although trans-cervical balloon catheter is used in some UK hospitals, outpatient use is not common. Hospital Episode Statistics (HES) database does not record the exact method of induction of labour, nor collect data on efficacy, cost-effectiveness, hospital stay or outcome of labour induction stratified according to the method of induction of labour. Therefore, there is no readily available data source that can be used to obtain information on the outcomes of induction of labour using mechanical methods in the outpatient setting.

We feel that a feasibility trial should be undertaken prior to embarking on a randomised controlled trial. This feasibility trial would permit collection of the variables of interest with sufficient precision so as to permit the design a future randomised controlled trial.

The primary outcome criteria are as follows:

Acceptability will be assessed by women's willingness to accept randomisation to a trial comparing the two methods in an outpatient context. Data will also be gathered on clinical outcomes including mode of birth, rate of labour and birth complications, admissions to NNU, maternal and infant morbidity and on women's experiences of induction using the different methods. In order to increase the external validity, we have selected two sites, one in inner-city London setting and the other, a typical UK district general Hospital.

Economic Evaluation

This feasibility trial will explore and model the measures needed to enable a full economic evaluation (cost consequences or cost-effectiveness approach) in a future RCT and test availability of needed data. This will also contribute to the power calculation for a future trial. Data items to be tested will include: time in the unit before return to home, numbers of phone or personal calls to the unit, rate of re-admissions prior to diagnosis of active labour, time from readmission to birth, time from admission to postnatal hospital discharge, number of further Propess administrations, rate of use of additional induction methods. There are no out-patient trials comparing balloon catheter with sustained release vaginal prostaglandin head-to-head. Therefore, such a study is needed. The use of either method may allow women to go home and remain at home over-night. The study has the potential to radically change induction of labour in the UK. The potential benefits to women and NHS:

1. If preferred by women, it will improve their experience of induced labour.

2. From previous published literature, hyper- stimulation does not occur with trans-cervical balloon use. This is likely to lead to lesser use of pain-relief.

3. By reducing the side effects of Prostaglandins (strong/more frequent contractions) it is likely to improve safety, particularly with out-patient use.

The potential benefits to the NHS are as follows:

1. The use of mechanical methods may be cheaper.

2. By allowing participants to spend more time at home, this method has the potential benefit of cost saving, and improvement in patient management and acceptability

Study Rationale and risk/benefit analysis

Assessment & management of potential risk

This trial is categorised as • IMP Type A = No higher than the risk of standard medical care. The IMP will be stored, prescribed and dispensed in accordance with the institutions' hospital policy.

The study will be conducted within 2 experienced maternity units where the low-risk eligible pregnant women will be randomised to receive either prostaglandin E2 10mg pessary (Propess) in accordance with the manufacturer's recommendations or Cook Cervical Ripening Balloon in accordance with the Technical data sheet. The women will be discharged home to return to the unit the following morning, or if in labour, whichever was earlier.

7. Trial design

7.1 Overall design

This study will randomise women at term (gestational age of > 37+ 0 weeks), and requiring induction of labour (IOL) to receive either Propess or Cook cervical ripening balloon.

For women who attend the antenatal unit for assessment and a cervical sweep at 41+0 weeks. Induction of labour (IOL) is recommended at this visit. If they agree, they are usually booked for induction of labour at 41+3 weeks. At this visit, written information will be provided to women regarding the available methods: IOL with sustained release Prostaglandins (Propess), or IOL using trans-cervical Cook balloon catheter both in outpatient setting. Women will be invited to participate in the study, where they will be randomised to the trans-cervical balloon catheter or the vaginal prostaglandin 10mg (Propess).

St Georges University Hospitals NHS Foundation Trust is a large teaching hospital located in Tooting, South London and Medway Hospital is a district general hospital just outside of M25. The sample size of 120, will be split over the two sites. Randomisation will take into account the fact that the study is multi-centric.

8. IMP Dosage regimen and rationale

8.1 IMPs and non-IMPs used in the trial

Name and description of IMP

Propess (Prostaglandin E2) 10mg vaginal inserts

Route of administration, dosage, dosage regimen, and treatment period(s) of the IMPs

The Propess Vaginal insert (10mg) should be administered high into the posterior vaginal fornix using only small amounts of water soluble lubricants to aid insertion. After the vaginal delivery system has been inserted, the withdrawal tape may be cut with scissors always ensuring there is sufficient tape outside of the vagina to aid removal. No attempt to tuck the tape inside of the vagina should be made as this can make retrieval more difficult. The woman should be recumbent for 20-

30 minutes following insertion. The delivery device is designed to release Prostaglandin (Dinoprostone) continuously over a period of 24 hours.

Following successful insertion and satisfactory assessment, the woman can be discharged home

8.2 Source of IMP

The following IMP will be sourced from routine hospital stock and their handling and management will be subject to standard procedures of the pharmacy.

Sustained release Prostaglandin Pessary 10 mg (Propess)

8.3 Accountability procedures for the IMP(s)

The Prostaglandin E2 vaginal pessary upon removal from the ward/unit stock freezer dispensation should be added to the participant's prescription chart in the maternity notes. A note of the Manufacturer, Batch number and Expiration date must be included in addition to the date and time of administration.

Time of discharge of woman should be added following the 20-30 minutes observation.

This information will act as Source data to be transcribed to the study Case Report Form

8.4 Assessment of compliance

The treatment is not self-administered. In the event that the vaginal pessary is expelled, the time of expulsion (if known) will be recorded in the maternity notes.

8.5 Name and description of each non-IMP (NIMP)

No NIMPs used.

8.6 Concomitant treatment

Propess pessary should not be used concurrently with oxytocic drugs.

Any pain relief prescribed during labour must be fully documented in the participant's maternity notes

8.7 Interventions involving a device

Cook cervical Ripening balloon

The Cook cervical Ripening balloon is a silicone double balloon catheter. Maximum balloon inflation is 80ml/balloon. Always inflate the balloon with sterile sodium chloride 0.9%.

The woman should be positioned in the lithotomy position and insert a vaginal speculum to gain cervical access. The cervix must be cleaned appropriately to prepare for device insertion. Insert the device into the cervix and advance until both balloons have entered the cervical canal. Inflate the uterine balloon with 40ml Sodium Chloride 0.9% using a standard luer lock 20ml syringe through the red check-flo valve marked U.

Once the uterine balloon is inflated, the device is pulled back until the balloon is against the internal cervical os. The vaginal balloon is now visible outside the external cervical os. Inflate the vaginal balloon with 20ml NaCl 0.9% using a standard luer lock 20ml syringe through the green Check-Flo valve marked V. Once the balloons are situated on each side of the cervix and the device is fixed in place, remove the speculum. Add more fluid to each balloon in turn, in 20ml increments until each balloon contains 80ml (maximum volume of fluid) Do NOT overinflate the balloons.

If necessary, the proximal end of the catheter may be taped to the patient's thigh.

- The lot number and time of insertion of the device must be recorded in the maternity notes. Also within this source documentation note the time of discharge of the participant.

To remove the device both balloons must be deflated through the corresponding valves marked U and V and removed vaginally. NB: If the membranes rupture spontaneously before removal of the device, it is recommended to deflate the balloons and remove the device to facilitate active labour management.

9. Participant Selection criteria

There will be no exceptions (waivers) to eligibility criteria prior to participant inclusion into the study. Any questions raised about eligibility should be addressed prior to entering the participant.

The eligibility criteria have been carefully considered and are standards used to ensure both the safety of the participants and that the trial results can be appropriately used to make future treatment decisions for other people with similar disease or medical condition. It is therefore vital exceptions are not made to the following detailed selection criteria. D*eviations from the eligibility criteria are considered to be protocol violation and may be reported to the MHRA as a serious breach*

All participants that are screened for inclusion into the study must be entered onto the Sponsor screening log JREOLOG0001 and will be assigned a sequential number. Participants will be considered eligible for enrolment into this trial if they fulfil all of the inclusion criteria and none of the exclusion criteria as defined below.

We will include women who are thought to be suitable for out-patient induction of labour based on existing guidelines at the two sites (St. George's Hospital and Medway Maritime Hospital).
Eligible participants will be entered onto the Sponsors Subject ID log JREOLOG0002 and assigned a Trial specific Identification number in a pre-agreed format in accordance with Site identifier and next sequential numerical value e.g. SG001 for St Georges and MW001 for Medway.

Inclusion criteria

1. Pregnant women with a single fetus and uncomplicated pregnancy, with a gestational age > 37+ 0 weeks, needing induction of labour
2. ≥18 years of age
3. No medical risk factors.

Exclusion criteria

1 Out-patient induction of labour is deemed unsuitable for the following women on the grounds of safety -

- Grand multiparous women (Parity 5 or more)
- Multiple pregnancy
- Women with complex medical or obstetric problems
- Previous caesarean section/uterine scar

2 Women who are contracting and/ or requiring analgesia
3 Women who do not fully understand the information leaflet and unable to provide full informed consent
4 Women for whom out-patient induction is unsuitable according to local hospital protocol

9 Subject/Patient Recruitment process

Patient recruitment at a site will only commence once evidence of the following are in place:

1. REC, HRA approval, and MHRA Confirmation of Trial notification
2. Signed Delegation of Duties and Sponsorship Agreement (JREODOC0013) returned to the Sponsor JREO
3. Final sponsorship (which may include evidence of Pharmacy Green light) issued by Sponsor representative of the JREO
4. The trial initiation procedure completed and the issue of the 'Open to recruitment' letter by the JREO

All sites participating in the trial will also be asked to provide a copy of the following:

1. Signed Clinical Trial Site Agreement (CTSA)/ Statement of Activities,
2. Host site Confirmation of Capacity and Capability

All subjects who wish to enter the study will be fully screened and consented by the Principal Investigator, or one of the qualified clinicians involved in the study as delegated by the PI.

Low-risk pregnant women at term needing induction of labour will be invited to participate in the study. If they agree, written information will be provided to women regarding the available methods: IOL with sustained release Prostaglandins, or IOL using trans-cervical balloon catheter both in outpatient setting.

The study will be conducted over two sites: St. George's Hospital in London, and Medway Hospital in Kent.

10 Study procedures

10.1 Informed consent

Please note, it is essential that all trial personnel/staff undertaking the informed consent process has signed the Sponsor's Delegation of Responsibilities Log JREOLOG0004 to ensure that the person has been delegated the responsibility by the study CI/PI. All personnel taking informed consent must be GCP trained. Refer to Sponsor SOP JREOSOP0027

Informed consent from the participant or legally authorised representative must be obtained following explanation of the aims, methods, benefits and potential hazards of the trial and before

any trial specific procedures are performed. The only procedures that may be performed in advance of written informed consent being taken are those that would have been performed on all participants in the same situation as routine clinical practice.

Informed written consent will be obtained by the site Principal Investigator or a nominated deputy as recorded on the Sponsor's Delegation of Responsibilities Log.

Consent to enter this study will be obtained after 37+0 weeks after a full account has been provided of its nature, purpose, risks, burdens and potential benefits. Patients will have the opportunity to consider whether they wish to take part in the study. For prolonged pregnancy (>41+0 weeks), Induction of labour is generally booked at 41+3 weeks, giving a 3-day time period to think about participation, although women may be provided with information about the study prior to this. Periods shorter than 72 hours will be permitted if the woman felt that further deliberation will not lead to a change in her decision, and provided the person seeking consent is satisfied that the woman has fully retained, understood and deliberated on the information given. This provision has been made with the support of our patient advisory group. Likewise, periods longer than 72 hours will be permitted should the woman request this. The Investigator or designee will explain that the woman is under no obligation to enter the trial and that she can withdraw at any time during the trial, without having to give a reason. A copy of the signed Informed Consent Form will be given to the study participant. The original signed consent form (ICF) will be retained at the study site in the ISF and a copy of the ICF along with a copy of the Participant Information Sheet (PIS) will be retained in the maternity notes.

For those women who provide consent to enter the study and indicate agreement to participate in the post-natal interview (which can last approximately 30 to 60 minutes) the midwife will encourage the woman to discuss the study with their birth partner as there will also be an option for the birth partner to participate in the post-natal interviews in addition to the woman to share their experiences. It will be made clear to the woman and to the birth partner that they should not feel obliged to participate in any way and their decision collectively or singularly not to participate, would not affect their ongoing care in any way.

If new safety information results in significant changes to the risk–benefit assessment, the consent form will be reviewed and updated if necessary. All subjects, including those already treated, will be informed of the new information, given a copy of the revised consent form and asked to re-consent if they choose to continue in the study.

10.2 Randomisation procedure

The randomisation of participants will be provided by King's Clinical Trials Unit (CTU). This will be an on-line service, and electronic access will be provided to the trial staff recorded on the study site delegation log. http://www.ctu.co.uk/ A user specific password will be provided for use on the website.

Randomisation and registration instructions:

a) Request user access for relevant site staff from the Chief Investigator.
b) Ensure an appropriate browser and stable internet connection is being used.
c) Go to www.ctu.co.uk and click 'Randomisation service'.
d) Select the PROBITF study from the list.
e) Enter username *(usually email address)* and password. If password is forgotten, click on 'Forgot my password?'

f) Select the 'randomisation tab' and click 'randomisation request', then click 'randomise'
g) Enter the participant's initials using the **second letter** each of the participant's given name, middle name (if applicable) and family name. For example: Jane May Smith would be entered as AAM, A participant without a middle name such as Anne Jones would be entered as N-O to ensure 3 characters are entered, use a hyphen. A hyphen can be used if the participant does not have a middle name.
h) Enter the participant's date of birth as **01/01/year of birth**. The day and month will always be entered as 01/01/xxxx, for example, date of birth 15/04/1990 would be entered as 01/01/1990.
i) Enter the date of consent.
j) If required, click the 'edit' button on relevant data fields, enter the data and then click 'save'
k) Once all information is entered and checked as correct, the participant is ready to randomise.

   ****NOTE errors cannot be corrected later. Once certain all data is correct and the participant is proceeding into the trial, the participant can be randomised****

l) Click the submit button once and wait for the system to confirm the randomisation is complete. Do not repeatedly click submit.
m) Check email inbox for randomisation confirmation email. File a copy of the randomisation confirmation email in the ISF
n) The exact details used to randomise the participant must be entered on to the eCRF Registration Form in exactly the same format, e.g. for Jane May Smith: initials: AAM, date of birth: 01/01/1990, and date of consent. For Anne Jones: initials N-O,

Troubleshooting:

o) Email confirmation is usually instantaneous. If email does not arrive, this can occasionally be due to local IT issues. Typically this merely results in a short delay. If you have waited a few minutes and the email still hasn't arrived, log back into the system, click randomisation tab and select randomisation history, click history and check the records to see if the participant was successfully randomised. If you are certain the participant was not successfully randomised (e.g. due to a power failure mid-randomisation) then begin the process again using the same identifiers and submit the randomisation request. Never randomise a participant more than once. Contact the trial manager if unsure whether the participant was successfully randomised or if the confirmation email has not arrived within half an hour of successfully submitting the randomisation request.

Any problems or technical issues encountered sites are advised to contact the Study site PI in the 1st instance – Contact details in Protocol Section 2.

In order to ensure a similar distribution between treatment groups in important characteristics thought to affect outcomes, including site and parity, allocation will be random and stratified by site (St. George's and Medway) and parity (nulliparous and multiparous). Participants will be allocated using block randomisation so as to ensure similar numbers of participants in the treatment groups. Balance of the randomised groups will be checked periodically by the trial statistician (Dr. Sedgwick).

Participants and midwives will not be blinded to the treatment allocation. The trial statistician will be blinded to group allocation. The trial will be analysed using an intention to treat approach.

10.3 Prescribing & Dispensing of IMP /Device

Dispensation of the Propess or Cook Balloon will be in accordance with routine clinical practice following intervention allocation and will be taken from Hospital stock/ antenatal unit supplies.

Trial specific labelling is not required. The Prostaglandin E2 (Propess) will be dispensed in accordance with a prescription given by an authorised healthcare professional and will be labelled in accordance with the requirements of Schedule 5 to the Medicines for Human Use (SI1994/3194) (Marketing Authorisations etc) Regulations that apply in relation to relevant medicinal products.

The treatment allocation/intervention will be recorded on the maternal notes of the participant together with full details of the relevant manufacturer, lot or batch number and time of administration. Additional observatory notes should also be annotated in the maternal notes.

10.4 Discontinuation/withdrawal of participants

- In consenting to the trial, participants are consenting to trial treatments, trial follow up and data collection. However, an individual participant may stop treatment early or be stopped early for any one of the following reasons:
- Unacceptable treatment toxicity or an adverse event
- Intercurrent illness that prevents further protocol treatment
- Any change in participant's condition that is in the investigator's opinion justifies the discontinuation of treatment
- Withdrawal of consent from the participant

As participation in the trial is entirely voluntary, the participant may choose to discontinue treatment at any time without penalties or loss of benefits to which they may be entitled. Although not obliged to give a reason for discontinuing their trial treatment/ protocol inclusion a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights. Participants who discontinue protocol treatment, for any of the above reasons, should remain in the trial for the purpose of follow up and data analysis.

The participant will be withdrawn from the study only if she withdraws consent.

With the participant's consent, the data collected till the time of withdrawal will be stored and used for final analysis. No additional data will be collected/stored for the purpose of the study.

Participants withdrawing consent for the trial will still need induction of labour. They will be managed according to the local hospital protocols for labour induction. No additional data will be collected/stored for the purpose of the study.

- Participants who stop the trial follow up early will not be replaced following receipt of the randomised intervention

10.5 Participant transfers

If a participant moves from the area making continued follow up at their consenting centre inappropriate, every effort should be made for them to be followed up at another Sponsor approved trial centre. Written consent should be taken at the new centre and then a copy of the participant's CRF should be provided to the new centre. Responsibility for the participant remains with the original consenting centre until the new consent process is complete. A sticker to flag that the patient is involved in the trial will be placed on the patient's maternity notes and an information sheet will also be filed in the front of the women's maternity notes.

10.6 Lost to Follow up

Community midwives looking after the participants will provide a home visit in the event the participant does not attend her scheduled return appointment following commencing the induction process.

10.7 Definition of the End of Trial

End of the trial will be defined as the Last data entry point.

The REC and the MHRA requires notification of the end of trial within 90 days of its planned completion or within 15 days if the study is terminated early. Refer to JREOSOP0015 and inform the JREO to facilitate assistance and compliance with requirements

11 Study Assessments

Following informed consent being documented the maternity notes should be annotated with details of the Trial, the information provided and consent documented. A study alert sticker should be added to the front of the maternity notes. No screening assessments beyond that which would occur during normal clinical assessment must take place prior to consent.

Survey
Recruitment Survey. Questionnaires will be given to all women at the point of recruitment. Women who decline study participation will be invited to complete the questionnaire anonymously and it will be **made clear that the aim of the survey is solely to improve future care through assessing the feasibility of the balloon catheter/Propess with no implications** for their own care. The survey will comprise closed questions plus comment boxes to examine women's understanding of the trial, their reasons for participation or declining. A detailed process log will also be maintained to identify the numbers and proportions of women who accept randomisation and those who withdraw after entry to the trial.

11.1 Screening assessments

Screening assessment will consist of a review of the potential participant's notes to ensure that inclusion criteria are satisfied, and also to make sure that there are no exclusion criteria.

11.2 Baseline assessments

Before entry to the trial, assessment of maternal blood pressure, pulse and respiratory rate, foetal assessment using a cardiotocograph (CTG foetal monitoring) are deemed as normal are required. Digital assessment of the cervix (Bishop Score) will be performed by the managing obstetrician or midwife according to hospital protocol.

The relevant trial staff on the delegation log will have electronic access to the online randomisation service and database. The minimum information for randomisation is the study centre, parity, gestational age, maternal age and confirmation that inclusion criteria are met and consent has been obtained.

The participant's study ID will be documented in the participant's maternity notes, consent form and case report forms (CRF).

Document participant study ID in the Source documentation / maternal notes together with the intervention to be administered. State: Propess or Cervical Balloon

11.3 Intervention

Induction of labour with Propess: 10mg insert will be introduced in the posterior vaginal fornix close to the cervix, using only small amounts of water soluble lubricants to aid insertion, as recommended by the manufacturer. After the vaginal delivery system has been inserted, the withdrawal tape may be cut with scissors always ensuring there is sufficient tape outside of the vagina to aid removal. No attempt to tuck the tape inside of the vagina should be made as this can make retrieval more difficult. The woman should be recumbent for 20-30 minutes following insertion. The delivery device is designed to release Prostaglandin (Dinoprostone) continuously over a period of 24 hours. Women will undergo monitoring of fetal condition and uterine activity by cardio-tocography (CTG) according to the existing protocol. It will be discontinued once the CTG is deemed to be normal. The woman will be allowed home with instructions to return to the hospital at an agreed time on the following morning, or if in labour, whichever was earlier. On the following morning/upon onset of labour the pessary will be removed, and artificial rupture of membranes (ARM) attempted (if spontaneous rupture has not occurred). If there has been insufficient ripening in 24 hours, the vaginal delivery system should be removed.

Induction of labour with balloon catheter: The woman should be positioned in the lithotomy position and insert a large vaginal speculum to gain cervical access. The cervix must be cleaned appropriately to prepare for device insertion. Insert the device into the cervix and advance until both balloons have entered the cervical canal. Inflate the uterine balloon with 40ml Sodium Chloride 0.9% using a standard luer lock 20ml syringe through the red check-flow valve marked U.

Once the uterine balloon is inflated, the device is pulled back until the balloon is against the internal cervical os. The vaginal balloon is now visible outside the external cervical os. Inflate the vaginal balloon with 20ml NaCl 0.9% using a standard luer lock 20ml syringe through the green Check-Flo valve marked V. Once the balloons are situated on each side of the cervix and the device is fixed in place, remove the speculum. Add more fluid to each balloon in turn, in 20ml increments until each balloon contains 80ml (maximum volume of fluid) Do NOT overinflate the balloons. If desired the end of the catheter may be taped to the woman's thigh. Women will undergo monitoring of fetal condition and uterine activity by cardio-tocography (CTG) according to the existing protocol. It will be discontinued once the CTG is deemed to be normal. The woman will be allowed home with instructions to return to the hospital at an agreed time on the following morning, or if in labour, whichever was earlier. On the following morning/upon onset of labour the device will be removed, and artificial rupture of membranes (ARM) attempted (if spontaneous rupture has not occurred).

To remove the device both balloons must be deflated through the corresponding valves marked U and V and removed vaginally. NB: If the membranes rupture spontaneously before removal of the device, it is recommended to deflate the balloons and remove the device to facilitate active labour management.

Subsequent Assessments

When the participant returns, the Propess/balloon catheter will be removed, and artificial rupture of membranes (ARM) attempted (if spontaneous rupture has not occurred).

If artificial rupture of membranes was not possible, this will be considered as treatment failure and alternative ways of achieving delivery will be sought as per local guidelines and followed. Unsuccessful placement of the balloon or inability to perform ARM will be considered as treatment failure and an alternative method of IOL will be used.

Follow-up questionnaire for participants: We will use a slightly modified form of questionnaire previously used by Henry et al (2013) to assess patient satisfaction, experience of participating, experience of the IoL process using either method including pain or discomfort, experience of outpatient IoL and level of information provided.

Qualitative study

In addition, qualitative data will be gathered for a sample of participants to enable a fuller exploration of the trial feasibility in two stages.

1. Research discussion (introduction & explanation of the study)

The aim of the qualitative study is to gain a better understanding of feasibility and effective trial procedures for a trial where interventions cannot be blinded and preferences may be strong. Researchers with experience of studies of trial processes, independent of the trial management, will (with consent of women and professionals) be sent audio-recordings* of a sample of research discussions to ascertain how information is provided and to understand in greater depth how choices about trial participation are made. A sample of research discussions will be audio-recorded with the consent of the participant and medical professional. It is believed that audio recording with both women and professionals' consent would be less intrusive than physical presence of a qualitative researcher and may facilitate a more realistic conversation. The focus will include diversity issues, as typically participation in RCTs is socially and ethnically skewed. This will be a consecutive sample continued until saturation to include women randomised to Propess/balloon, those women who decline and a cross-section of social and ethnic groups. Estimated sample size: 40. Women may wish to be accompanied by a friend or relative (e.g. birth partner) during this discussion. If so, the person accompanying the woman will also be asked for their consent (a copy of this consent will be given to the friend/relative and the original will be kept in the ISF, a copy will NOT be placed the medical records).

*Audio-recordings will be transferred to City, University of London via a controlled access OneDrive file. No identifiable information will be added to the audio file. Audio-recordings will be transcribed without containing any directly identifiable information, although direct quotes may be used. Once transcribed, the audio-recordings will be securely destroyed. Transcriptions will not be added to participants' medical records. Qualitative analysis of the audio files will be supported using the NVivo Version-11.3.2. qualitative data analysis software.

2. Post-natal semi-structured interviews – Conducted by City, University of London

All Women who consented to participate in the trial will be invited to participate in semi-structured interviews postnatally, to explore their experience of participating and of the IoL process using either method, their experience of outpatient IoL and any further reflections. The semi-structured interviews will last approximately 30 to 60 minutes and will be audio-recorded**. Those who provide telephone details will be contacted postnatally to confirm whether they are still happy to participate in an interview, following checks of neonatal outcomes. The interviews can be conducted by telephone or at a location convenient to the participant (e.g. her home) if preferred. Women may complete the interview alone or with their birth partner. All women, birth partners (if applicable) and professionals will be assured of confidentiality and their rights to decline consent. A thematic framework analysis will be conducted focused on lessons for trial feasibility, design, recruitment and retention, and patient experiences of cervical ripening using either method for induction in an outpatient setting. This approach enables consideration of unintended as well as anticipated consequences plus a fuller understanding of how women and their birth partners experience induction of labour and whether an outpatient approach confers advantages in terms of experience and satisfaction since, despite this being a key rationale for an outpatient approach, patient experiences of different induction approaches is an under-explored area. The number of interviews will be guided by data saturation, with a maximum potential sample of 40.

** Audio-recordings will be made by City, University of London. No identifiable information will be added to the audio file. Audio-recordings will be stored securely on a OneDrive file and transcribed without containing any directly identifiable information, although direct quotes may be used. The transcriber(s) complete a confidentiality agreement to ensure non-disclosure of data. Once transcribed, the audio-recordings will be securely destroyed. Transcriptions will not be added to participants' medical records.

3. Midwifery interviews - Conducted by city, University of London

Understanding the acceptability of the research design is an essential component of any feasibility trial. Since midwives are responsible for delivering the majority of care to women during pregnancy, birth and in the days following the birth, a sample of midwives involved in the delivery of maternity care at both sites, during any point in the trial – antenatal, intra partum or postpartum – will be invited to participate in one semi-structured interview. These interviews will explore the midwife's experience of supporting participating women in the IoL process using either method, their opinions of the feasibility of a full RCT in outpatient IoL, any further reflections on the research process and their involvement in it.

All interviews will take place face-to-face at a mutually convenient time and place. When and if necessary the researcher will follow the Lone Worker Procedure from City, University of London (SP40). The interviews will be digitally recorded and later transcribed verbatim. All data audio and written, will be stored and archived (NB: recordings are destroyed once transcribed, see below) at City, University of London in accordance to their research governance procedure, on their secure Onedrive. Each interview is estimated to take between 30 – 60 minutes.

The research midwives at both clinical sites involved in the trial will initially act as the recruitment gatekeepers. Only those midwives who have been previously approached by the research midwives will be invited to take part in the interview. Snowball sampling (chain or network sampling) from recommendations made during the qualitative, semi-structured interviews will then be used to access the remainder of the sample. It is estimated that between 5 - 20 midwives will take part in the semi-structure interview.

All potential participants will be provided with an information sheet prior to their participation. The information sheets will be distributed by the research midwives at both sites. All potential participants will be given a minimum of a week to decide whether they wish to take part. Verbal and written explanations will be provided to ensure that all midwifery participants understand that

their participation is voluntary and that they can withdraw themselves and or their data from the study at any point up to the point of data anonymisation.
Analysis of these data will be conducted using NVivo Version-11.3.2. taking a thematic analysis approach focused on lessons learned from trial feasibility in terms of its acceptability to staff, design, recruitment and retention, and staff experiences of caring for women with cervical ripening using either method for induction in an outpatient setting. Audio data will be destroyed after analysis. Interview transcripts will be archived for a minimum of 10 years as per City, University of London research governance protocol.

12 Safety and Pharmacovigilance

The following definitions and instructions should be used for both **IMP and device events**:

12.1 Definitions

Adverse Event (AE)—any untoward medical occurrence in a patient or clinical trial subject who is administered an IMP and which does not necessarily have a causal relationship with this treatment which may include an exacerbation of a pre-existing illness; increase in frequency or severity of pre-existing episodic condition; a condition (regardless of whether present prior to the start of the trial) that is detected after trial drug administration. (This does not include pre-existing conditions recorded as such at baseline or a continuous persistent disease.)

Adverse Reaction (AR)—any untoward and unintended responses to an IMP related to any dose administered.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)—any Adverse Event or Reaction that at any dose:

- Results in death; or
- Is life-threatening (places the subject, in the view of the Investigator, at immediate risk of death)
- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay; even if it is a precautionary measure for observation; including hospitalisation for an elective procedure, for a pre-existing condition)
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions)
- Consists of a congenital anomaly or birth defect (in offspring of subjects or their parents taking the IMP regardless of time of diagnosis).
- Or is another important medical condition

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the outcomes listed in the definition of serious will also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR)—an Adverse Reaction which is classed in nature as both serious and unexpected.

An 'Unexpected Adverse Reaction' is when both the nature and severity of the event is not consistent with the reference safety information available for the IMP in question.

12.2 Investigator responsibilities relating to safety reporting

All Adverse Events whether serious or not will be recorded in the hospital notes in the first instance. A record must also be kept in the participant's CRF and the Sponsor's AE Log JREOLOG0007.

The PROBIT-F reporting period for safety reporting will be up to 72 hours following administration of the randomised study intervention or as long as the study intervention is in situ, whichever is longer.

SAEs and SARs must be notified to the sponsor immediately the investigator becomes aware of the event (within 24 hours). Refer to JREOSOP0006 and ensure the completed SAE report form JREODOC0012 is sent to the sponsor via fax on 020 8725 0794 or E-mailed to adverseevents@sgul.ac.uk,

For any *SAEs that occur in relation to the insertion or use of the Cook Balloon Catheter* **in addition** to following the reporting instructions in the paragraph above the PI MUST report the incident to the Cook Medical Europe Ltd via telephone 00 353 61 334440 and request their medical safety officer. This report must occur within 2 days of the event. It is advised that the SAE report form JREIODOC0012 is completed and faxed additionally to 00 353 61 334441. You may be required to complete a manufacturer specific report. You must oblige. A copy of the completed manufacturers form should also be provided to the Sponsor as above.

The Sponsor will notify all SUSARs to the MHRA electronically utilising the eSUSAR system. And the REC via email.

The Sponsor will inform the MHRA and the REC of fatal or life threatening SUSARs as soon as possible, but no later than 7 calendar days after the receipt of the SAE report form. Any additional information will be reported within 8 days of sending the initial report.

The Sponsor must report all other SUSARs and safety issues to the MHRA and REC, as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting.

Causality Assessment—must be made by a medically qualified doctor as these decisions require medical and scientific judgment as well as knowledge of the participant concerned. The investigator must assess the causality of all SAEs or SARs in relation to the IMP using the following descriptions:

Definitely—there is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

Probably—there is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

Possibly—there is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (i.e. the patient's clinical condition, other concomitant events).

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 trial medication). There is another

reasonable explanation for the event (e.g. the participant's clinical condition, or other concomitant treatments).

Unrelated—there is no evidence of any causal relationship.

Not Assessable – note - if this description is used the sponsor will assume the event is related to the IMP until follow up information is received from the investigator to confirm a definitive causality assessment

Any SUSAR assessed as related to the IMP will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

Expectedness should be based solely on the available RSI for the IMP and will be described using following categories:

Expected—an AE that is classed in nature as serious and which is consistent with the information about the IMP listed in the RSI or clearly defined in this protocol.

Unexpected—an AE that is classed in nature as serious and which is not consistent with the information about the IMP listed in the RSI

The completed AE Log JREOLOG0007 will be sent to Sponsor upon request and/or every 2 months.

The Chief or Principal Investigator will respond to any SAE queries raised by the Sponsor as soon as possible. Follow up reports must continually be completed within acceptable time-frames and sent to the sponsor as detailed above until the reportable event is considered resolved.

All IMPs used in this trial are licensed in the UK and used within their marketing authorisation, **expected** SARs are outlined in the most recent SmPCs and listed below: –

Balloon catheter:
Spontaneous rupture of membranes, device entrapment/fragmentation, maternal discomfort during and/or after insertion, device expulsion, cervical laceration or bleeding, failed dilatation, Caesarean section, placental abruption, uterine rupture, spontaneous onset of labour.

Propess:
nausea, vomiting, diarrhoea; other side-effects include uterine hypertonus, severe uterine contractions, pulmonary or amniotic fluid embolism, abruptio placentae, foetal distress, maternal hypertension, bronchospasm, rapid cervical dilation, fever, backache, uterine hyper-contractility with or without foetal bradycardia, low Apgar scores; cardiac arrest, uterine rupture, stillbirth or neonatal death also reported, vaginal symptoms (warmth, irritation, pain)

The above SARs will only be recorded in the subjects' source data (hospital notes) and in the CRF exception- still births/neonatal deaths.

'Hospitalisation' for onset of labour will not be recorded as an SAE for admission to the Labour Ward/Delivery suite following the study intervention for IoL

Where the trial is conducted across multiple sites the collaborating PIs should ensure that all SAE reports are sent to the Sponsor (and device manufacturer where applicable) The Sponsor will ensure the CI is aware (where not coped into an email) and informed to facilitate evaluation and sign off.

The CI working collaboratively with the Sponsor will ensure that all collaborating PIs are kept informed of events that occur. Reports will be sent to the TSC for review every 6 months.

12.3 Notification of deaths

All deaths including neonatal and stillbirth will be reported to the Sponsor irrespective of whether the death is related to the intervention or an unrelated event. The death will be reported immediately.

12.4 Development Safety Update Reports (DSURs)

The CI or a delegated PI will prepare the DSUR, using the Sponsor's template and in accordance with the Sponsor's DSUR SOP JREOSOP0008. It will be reviewed by the Sponsor and when necessary be referred to an independent committee (i.e. Research Governance Safety Committee). The sponsor will provide the REC and the MHRA with the prepared DSUR at least annually and within the defined reporting timelines.

12.5 Annual Progress Reports (APRs)

The Chief Investigator will prepare the APR in accordance with JREOSOP0043. Following review by the sponsor the report will be sent to the REC. The APR is due for submission annually within 30 days of the anniversary date on which the favourable opinion was given by the Ethics committee, until the trial is declared ended.

12.6 Reporting Urgent Safety Measures

The Sponsor and Investigator may take appropriate urgent safety measures in order to protect the participants against any immediate hazard to their health or safety. If such measures are taken the Sponsor shall immediately or no later than 3 days from the date the measures are taken give written notice to the MHRA and REC of the measures taken and the circumstances given rise to such measures. The CI must notify the Sponsor immediately to facilitate compliance with the regulations. The Sponsor together with the CI will ensure that all collaborating PIs at participating sites are informed immediately of any urgent safety measures and the circumstances to facilitate appropriate management of participant safety.

Refer to sponsor SOP Management of Amendments JREOSOP0011 for guidance

12.7 Notification of Serious Breaches of GCP and/or the protocol

Any Protocol Deviations, Violations will be documented using JREODOC0061, and entered onto the Sponsor's log JREOLOG0005. Potential Serious Breaches and Urgent Safety Measures will be recorded both on the Sponsor's Log JREOLOG0005 and processed according to JREOSOP0012 and where necessary JREOSOP0032

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

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

(b) The scientific value of the trial.

The CI will notify the Sponsor immediately of any case where there exists a possible occurrence of a serious breach

13 Data management and quality assurance

13.1 Confidentiality

All data will be handled in accordance with the Data Protection Act 2018.

The Case Report Forms (CRFs) will not bear the participant's name or other directly identifiable data. The participant's trial Identification Number (ID) only, will be used for identification. The Sponsor Subject ID log JREOLOG0002 can be used to cross reference participant's identifiable information.

13.2 Data collection tool

Case Report Forms will be designed by the CI and the final version will be approved by the Sponsor. All data will be entered legibly in black ink with a ball-point pen. If the Investigator makes an error, it will be crossed through with a single line in such a way to ensure that the original entry can still be read. The correct entry will then be clearly inserted. The amendment will be initialled and dated by the person making the correction immediately. Overwriting or use of correction fluid will not be permitted.

It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the CRFs. The Staff Delegation of Responsibilities Log JREOLOG0004 will identify all trial personnel responsible for data collection, entry, handling and managing the database.

Data will be collected and recorded directly onto the electronic CRF by research staff when possible. It will be recorded in the medical notes and then transcribed onto electronic CRF when access to electronic CRF may not be possible, or the data form part of clinical documentation.

The participant satisfaction questionnaire is modified from a previously published one (Henry et al, 2012). Participants may be contacted by telephone if the data are missing.

13.3 Data handling and analysis

The Data base and Data Management plan will be created and managed by Kings Trials Unit.

Quality Control should be applied at each stage of data handling to ensure that all data are reliable and have been processed correctly.

14 Archiving arrangements

The trial essential documents along with the trial database will be archived in accordance with the Sponsor SOP JREOSOP0016. The agreed archiving period for this trial will be 15 years and will also be defined within the Delegation of Duties Sponsorship Agreement JREODOC0013.

Each PI at any participating site will archive the trial essential documents generated at the site for the agreed archiving period in accordance with the signed Clinical Trial Site agreement/Statement of Activities

15 Statistical design

15.1 Statistical input in trial design

Dr Philip Sedgwick, Reader in Medical Statistics at St. George's University of London, is a co-applicant. Sample size and recruitment He has contributed to the design of the study, plus advised on the sample size and recruitment.

King's clinical trials unit will provide a web randomisation service and design an electronic study database for data collection. *Electronic access will be provided to the site* Research Study *staff.*

Randomisation will be stratified by the site (SGH and Medway) and will be in permeated blocks in order to keep the proportion of parous women balanced.

Participants opting out of the trial will not be replaced, since this is a trial on acceptability. The study is not blinded.

Allowing for incomplete data and protocol violation, it is predicted that data from approximately 120 women will available and provide a sufficient sample size in order to consider the acceptability of randomisation to method of induction of labour for a future trial.

15.2 Endpoints

15.2.1 Primary endpoint

End of the study is defined as the last data entry point.

15.3 Sample size and recruitment

15.3.1 Sample size calculation

The study is planned as a feasibility trial. In particular the aim is to establish the willingness of women to be randomised, plus the acceptability of the balloon catheter. The results of this trial may inform future trials. Hence no formal sample size calculation was performed. It is anticipated that approximately 120 women will be recruited within the planned period of 12 months. Recruitment will be across two sites (St. George's and Medway). The proposed sample size was considered to be large enough to provide information on the key measures with sufficient accuracy, allowing for women withdrawing consent and without complete data. A multicentre trial was proposed to provide information on the feasibility of running a future trial plus acceptability of the balloon catheter for women living in very different demographic areas.

The study is planned as a feasibility trial no formal sample size calculation was performed.

15.3.2 Planned recruitment rate

The number of women that would be willing for randomisation and recruitment in the proposed study period cannot be predicted. At St. George's Hospital we currently have a delivery rate of 5000/year (400/month) and a 20% induction of labour rate. We expect 70-80 women / month to

undergo induction of labour, and 35-40 women/month undergoing induction of labour for prolonged pregnancy. We expect a similar number at Medway Maritime Hospital. It is proposed that the study period is of 12 months. In a previous patient survey 7 out of 10 women felt that random allocation is acceptable. Not all will be willing to take part in the trial. With a conservative estimate that 1 out of 8 women would be willing to participate (12.5%, five women/month) from each of the 2 sites.

15.4 Statistical analysis plan

15.4.1 Summary of baseline data and flow of patients

The number of eligible patients for the trial, the number consenting and the number randomised. Also a breakdown for each group of the numbers of participants assigned, receiving the intended treatment, completing the study protocol, and analysed for the primary outcome will be recorded. This information will be displayed as a flow diagram

Primary endpoint analysis

As a feasibility trial, the primary endpoint analysis will be evaluating and testing the trial processes per se, including acceptability of the balloon catheter, and not the effectiveness of the intervention. The analysis will be principally descriptive based on the independent treatment groups, with a focus on estimating parameters for a future trial, rather than hypothesis driven. There are no plans for predefined subgroup analysis. Analyses will be based on intention to treat. If data is missing then it will not be imputed, since one of the aims of the trial is to report on the extent of missing data and explore the feasibility of a future trial.

15.5 Randomisation

The trial management group will review randomisation each month, and report the recruitment number to the steering committee. In order to ensure a similar distribution between treatment groups in important characteristics thought to affect outcomes, including site and parity, allocation will be random and stratified by site (St. George's and Medway) and parity (nulliparous and multiparous). Participants will be allocated using block randomisation so as to ensure similar numbers of participants in the treatment groups.

15.6 Interim analysis

No interim analysis is planned.

15.7 Other statistical considerations

Not applicable

16 Direct access to source data

The Investigator(s)/institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

17 Site approval and ongoing Regulatory compliance

Before any site can enrol patients into the trial, the Principal Investigator must ensure written permission to proceed has been granted by that Trust Research & Development (R&D). The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and, by the regulatory authority/ies as appropriate and which was given favourable opinion by the Research Ethics Committee (REC) and HRA.

The Chief Investigator will be provided (via the Sponsor) with file indexes i.e. JREODOC0003 TMF index and JREODOC0004 ISF index for use with SOP JREOSOP0019 'Preparation and Maintenance of the TMF' The CI will be responsible for the maintenance of the TMF and will delegate the responsibility of ISF file maintenance to the PI at each participating site.

It is the responsibility of the Principal Investigator at each site to ensure that all subsequent amendments gain the necessary approval. Refer to JREOSOP0011 'Management of Amendments'. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients (see section 12.6 for details of reporting procedures/requirements).

Within 90 days after the end of the trial, the CI and Sponsor will ensure that the REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial. Refer to JREOSOP0015 'End of study declaration'

The CI will supply an End of Study report of the clinical trial to the MHRA and REC within one year after the end of the trial. The sponsor can provide JREODOC0059 End of study Report template

18 Monitoring plan for the trial

The CI will be requested to complete the JREODOC0032 Risk Assessment Questionnaire and forward to the Sponsor to facilitate appropriate costing and Sponsorship in Principle to be issued prior to REC application.

The trial will be monitored according to the risk based monitoring plan JREODOC0030 agreed by the Sponsor. It is the responsibility of the CI to ensure that the Sponsor's self-monitoring template is completed and submitted as instructed (refer to the Study Monitoring Plan for detail). The JREO governance team will determine the initial project risk assessment and justify change as the study progresses.

The PI at each collaborating site in addition to site monitoring visits may also be required to complete self-monitoring form(s) and must return the form to the sponsor for review and action. Failure for any PI to comply with requests for on behalf of the sponsor may be escalated in accordance with JREOSOP0031 Escalation Procedure; the site may also be selected for a GCP audit.

It is the Sponsor's responsibility to ensure that any findings identified in any monitoring report are actioned appropriately and in a timely manner and that any violations of GCP or the protocol will be reported to the CI & Sponsor representative. Any serious breach will be handled according to JREOSOP00032 Serious Breach Reporting

The CI will be provided with a copy of the study monitoring plan during the Trial Initiation monitoring visit.

19 Finance

This study has been awarded an NIHR RfPB grant (Ref. No. PB-PG-0815-20022)

20 Insurance and indemnity

NHS bodies are liable for clinical negligence and other negligent harm to individuals covered by their duty of care. NHS Institutions employing researchers are liable for negligent harm caused by the design of studies they initiate.

21 IP and development policy

Unless otherwise specified in agreements, the following guidelines shall apply: All Intellectual Property Rights and Know How (IP) related to the Protocol and the Trial are and shall remain the property of the Sponsor excluding

1) pre-existing IP related to clinical procedures of any Hospital.

2) pre-existing IP related to analytical procedures of any external laboratory.

All contributors

shall assign their its rights in relation to all Intellectual Property Rights and in all Know How, not excluded above to the Sponsor and at the request and expense of the Sponsor, shall execute all such documents and do all such other acts as the Sponsor may reasonably require in order to vest fully and effectively all such Intellectual Property Rights and Know How in the Sponsor or its nominee.

shall promptly disclose to the Sponsor any Know How generated pursuant to this Protocol and not excluded above and undertake treat such Know How as confidential information jointly owned between it and the Sponsor

Nothing in this section shall be construed so as to prevent or hinder and medical professional from using Know How gained during the performance of the Trial in the furtherance of its normal business activities, to the extent such use does not result in the disclosure or misuse of Confidential Information or the infringement of any Intellectual Property Right of the Sponsor.

22 Publication policy

Publication: “Any activity that discloses, outside of the circle of trial investigators, any final or interim data or results of the Trial, or any details of the Trial methodology that have not been made

public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations."

All scientific contributors to the Trial have a responsibility to ensure that results of scientific interest arising from Trial are appropriately published and disseminated. The Sponsor has a firm commitment to publish the results of the Trial in a transparent and unbiased manner without consideration for commercial objectives.

To maximise the impact and scientific validity of the Trial, data shall be consolidated over the duration of the trial, reviewed internally among all investigators and not be submitted for publication prematurely. Lead in any publications arising from the Trial shall lie with the Sponsor in the first instance.

22.1 Before the official completion of the Trial

All publications during this period are subject to permission by the Sponsor. If an investigator wishes to publish a sub-set of data without permission by the Sponsor during this period, the Funder shall have the final say.

Up to 180 days after the official completion of the Trial

During this period the Chief Investigator shall liaise with all investigators and strive to consolidate data and results and submit a manuscript for peer-review with a view to publication in a reputable academic journal or similar outlet as the Main Publication.

- The Chief Investigator shall be senior and corresponding author of the Main Publication.
- Insofar as compatible with the policies of the publication outlet and good academic practice, the other Investigators shall be listed in alphabetic order.
- Providers of analytical or technical services shall be acknowledged, but will only be listed as co-authors if their services were provided in a non-routine manner as part of a scientific collaboration.
- Members of the Steering Group shall only be acknowledged as co-authors if they contributed in other capacities as well.
- If there are disagreements about the substance, content, style, conclusions, or author list of the Main Publication, the Chief Investigator shall ask the Steering Group to arbitrate.

22.2 Beyond 180 days after the official completion of the Trial

After the Main Publication or after 180 days from Trial end date any Investigator or group of investigators may prepare further publications. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least sixty (60) days prior to submission for publication, public dissemination, or review by a publication committee. Sponsor's reasonable comments shall

be reflected. All publications related to the Trial shall credit the Chief and Co-Investigators as co-authors where this would be in accordance with normal academic practice and shall acknowledge the Sponsor and the Funders.

23 Statement of compliance

The trial will be conducted in compliance with the protocol, Sponsor's Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws and statutes of the UK country in which the study site is located including but not limited to, the Human Rights Act 1998, the Data Protection Act 2018, the Human Medicines Regulations 2012, the Medicines for Human Use (Clinical Trial) Regulations 2004, and with all relevant guidance relating to medicines and clinical studies from time to time in force including, but not limited to, the ICH GCP**,** the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version), the NHS Research Governance Framework for Health and Social Care (Version 2, April 2005).

This study will be conducted in compliance with the protocol approved by the REC and according to GCP standards and UK Clinical Trials Regulation. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and REC except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the Sponsor and REC as soon as possible.

24 List of Protocol appendices

Appendix 1 Protocol Amendment/Revision History (chronological order)

Appendix 2 Summary chart of study assessments

Appendix 3 Study Flow chart

25 References

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Appendix 1

Protocol amendment /Revision History

Protocol Version and Date Amendment type (Substantial/non-substantial) and Number	Details
NSAM01_AM01 Protocol v1.1 31/08/17	Section 10.2: Additional instructions for randomisation and registration of participants.
	Section 11.3: Clarification on interventions.
	Section 12: Clarification that definitions apply to both IMP and device.
SAM02_AM04 Protocol v2.0 20/12/17	Details added in section 10 regarding obtaining consent of the birth partner and section 11 pertaining to the audio recordings of the research discussion and the timing of the telephone interview. Refinement of inclusion criteria Synopsis and section 9 in line with Hospital IOL policy
SAM03_AM05 Protocol V3.0 23/05/2018	Signature page & Section 3: Change of Sponsor Representative
	Section 2: Trial Management Group and Trial Steering Committee members updated.
	Section 10: Clarification on when women may receive the PIS.
	Section 11.3 – Qualitative study: Further clarification on audio-recordings – women may be accompanied during research discussion audio-recordings & consent will be sought from accompanying person; transfer, transcription and subsequent destruction of audio-recordings.
	Section 11.3 – Post-natal semi-structured interviews: Addition of audio-recording; patient may be accompanied by birth partner & consent will be sought from birth partner; transfer, transcription and subsequent destruction of audio-recordings.

	Section 11.3 - Midwifery interviews: Addition of Midwifery interviews
	Section 12.2: Reporting frequency added for TSC review – 6 monthly.
	Appendix 2: Table updated for clarity and to remove errors.
	Correction of other minor typographical errors.

Appendix 2. *Summary chart of study assessments:*

Study Procedures	37 WEEKS 0/7 – 41 WEEKS 0/7	Screening	Randomisation	During treatment (Propess/ Balloon insertion):	Upon return to ward/when in labour	Follow up *(within 24 hours of delivery)*	Follow up
Recruitment/ research discussion recording (if consented to)	X						
Decliners questionnaire (if applicable)	X						
Informed consent (main study consent)	X						
Inclusion/exclusion criteria		X					
Medical history		X					
Demographics		X					
Randomisation via Kings CTU			X				
Satisfaction Questionnaire						X	
Study Intervention (Propess or Cook Device)			X				
Concomitant Medication		X					
Fetal Monitoring (CTG*)		X		X	X		
Semi-structured Interview (post-natal) & consent							X

*CTG frequency will be performed as per local protocol.

Appendix 3.

Women assessed for Trial suitability

Inclusion criteria

1. Pregnant women with a single fetus and uncomplicated pregnancy, with a gestational age > 37+ 0 weeks, needing induction of labour (IOL)
2. ≥18 years of age
3. No medical risk factors.

Exclusion criteria

1. Out-patient induction of labour is deemed unsuitable for the following women on the grounds of safety
   - Grand multiparous women (Parity 5 or more)
   - Multiple pregnancy
   - Women with complex medical or obstetric problems
   - Previous caesarean section/uterine scar
2. Women who are contracting and/ or requiring analgesia
3. Women who do not fully understand the information leaflet and unable to provide full informed consent
4. Women for whom out-patient induction is unsuitable according to local hospital protocol