This trial protocol has been provided by the authors to give readers additional information about their work.

Outpatient elective induction of labor at 39 weeks: The HOME INDUCTION RCT

This supplement contains the following items:

1. Original protocol (including a SAP)
2. Final protocol (including a SAP)
3. Summary of changes made from first to final protocol
4. Final SAP with more detailed information

Study Title

Full title of trial	The Home Induction trial: A randomised open-label trial to assess outpatient induction of labour, and compare efficacy of Propess vs Dilapan-S® for induction of labour at 39 weeks' gestation in normal risk nulliparous women.
Short title	IND HOME trial
Version and date of protocol	Version 1, 13-Jul-2020
Sponsor:	Rotunda Hospital
Funder (s) :	Rotunda Hospital
EudraCT no	2019-004697-25
ACTIVE IMP(s):	Propess; Dilapan-S
Dilapan-S®	
PLACEBO IMP(s):	None
Phase of trial	Phase 4
Sites(s)	Rotunda Hospital

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4. List of abbreviations

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CS	Caesarean Section
CTA	Clinical Trial Authorisation
CTG	Cardiotocograph
CTIMP	Clinical Trial of Investigational Medicinal Product
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
EMEA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IOL	Induction of labour
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
MA	Marketing Authorisation
PI	Principal Investigator
PIL	Participant Information Leaflet
QA	Quality Assurance

QC	Quality Control
QP	Qualified Person for release of trial drug
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

7. Summary

Title:

The Home Induction trial: A randomised open-label trial to assess efficacy of inpatient vs outpatient induction of labour, and compare efficacy of Propess vs Dilapan-S® for induction of labour at 39 weeks' gestation in normal risk nulliparous women.

Short title:	The Home Induction trial: Efficacy of outpatient induction of labour at 39 weeks with Dilapan-S® vs Propess
Trial medication:	**Propess** Dinoprostone 10mg vaginal delivery system. The insert contains 10mg dinoprostone which is released over 24 hours. **Dilapan-S®** is an osmotic hygroscopic dilator produced from a patented Aquacryl hydrogel.
Phase of trial:	Phase IV
Objectives:	**Primary objective(s):**

To demonstrate non-inferiority of efficacy for Dilapan-S® (12 hours or 24 hours insertion) to Propess for outpatient induction of labour at 39 weeks' gestation in otherwise uncomplicated, normal risk* nulliparous women.

To demonstrate non-inferiority of efficacy for Dilapan-S® 12-hour insertion to Dilapan-S® 24-hour insertion for outpatient induction at 39 weeks' gestation in otherwise uncomplicated, normal risk nulliparous women.

* A pregnancy is considered "normal-risk" when there are no active complications and there are no maternal or fetal factors that place the pregnancy at increased risk for complications. Specifically, the following conditions should be met to consider a pregnancy to be normal risk:

- Singleton pregnancy
- Cephalic presentation
- Term gestation (37-42 weeks gestational age)
- Maternal pre-pregnancy body mass index < 35kg/m2
- Maternal age of ≥ 18 and < 40 years
-

- No evidence of the following conditions:
    - Pre-pregnancy diabetes
    - Gestational diabetes
    - Pre-pregnancy hypertension
    - History of preterm birth
    - History of prior poor pregnancy outcome
    - History of a prior caesarean delivery
    - Cervical cerclage in situ
    - Premature rupture of membranes
    - Congenital fetal anomalies

Population: Normal risk nulliparous women with no medical complications who have no contraindications to induction of labour.

Secondary outcomes: Differences between groups will be measured for the following outcomes:

1. Overall change in Bishop score before and after cervical ripening
2. Rates of vaginal delivery at 36 hours after insertion of either Propess or Dilapan-S®
3. Rates of vaginal delivery at 24 hours after insertion of either Propess or Dilapan-S®
4. The need for second induction modality
5. Rates of hyper-stimulation
6. Rate of failed induction
7. Overall length of stay in hospital
8. Rates of adverse neonatal outcome
9. Rates of adverse maternal outcomes
10. Maternal satisfaction scores with the outpatient induction process
11. Caesarean delivery rates, categorized by “overall rate”, “rate for failure to progress/failed induction”, and “rate for non-reassuring fetal testing”
12. Analgesia use in each group, including rates of epidural
13. Compare rates of 39 weeks’ successful vaginal delivery in the outpatient setting to published rates of successful vaginal delivery in the inpatient setting.

Type of trial: A Phase IV trial in normal risk nulliparous women at 39 weeks' gestation.

Trial design and methods: A randomised open-label trial to assess and compare efficacy of Propess vs Dilapan-S® for induction of labour at 39 weeks' gestation in normal risk nulliparous women. Additionally, noninferiority will be compared in the Dilapan-S® 24 hour arm versus Dilapan-S® 12 hour arm.

Trial duration per participant:	8 weeks
Estimated total trial duration:	24 months
Planned trial sites:	Single-site
Total number of participants planned:	465

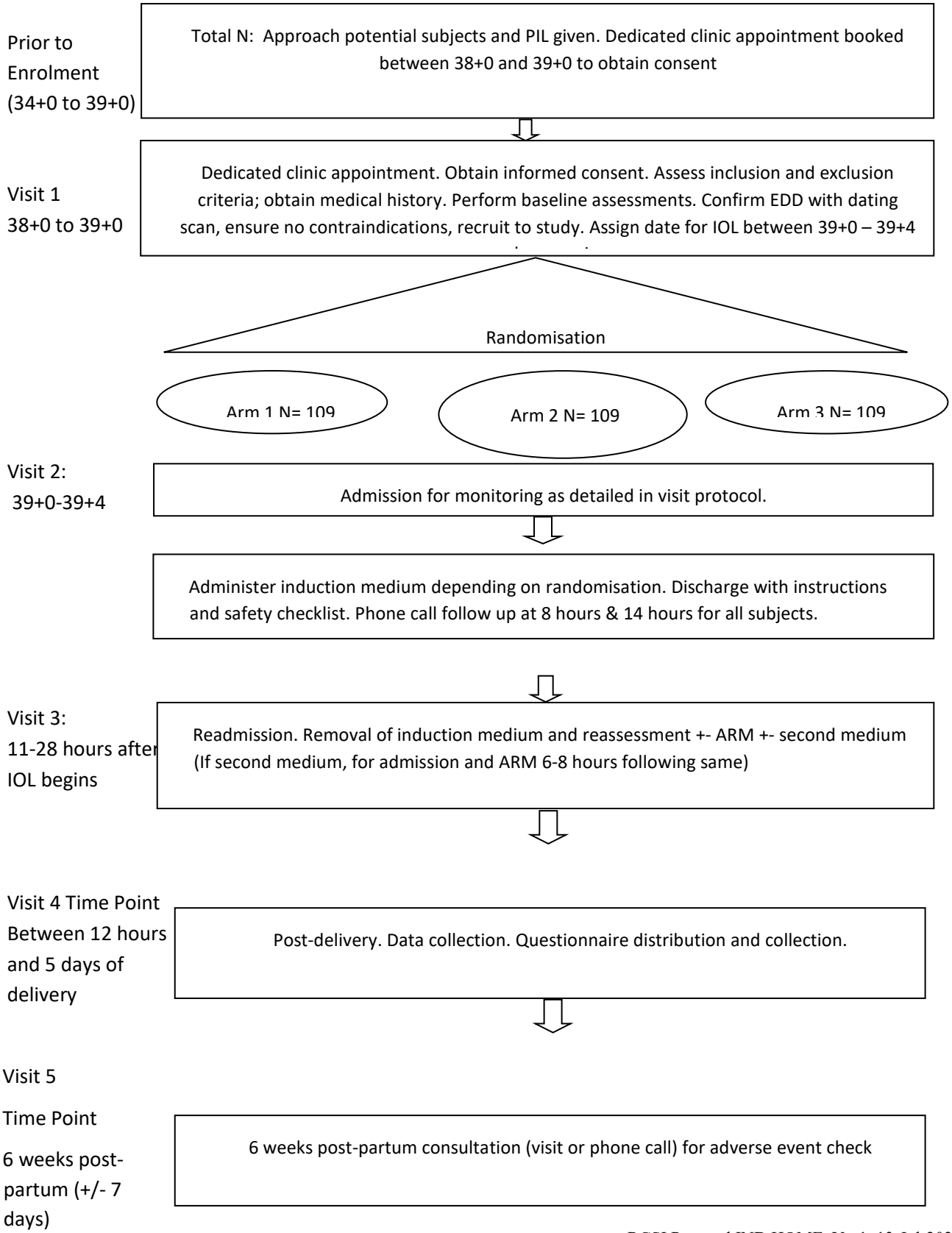
- **Inclusion criteria**
  - Normal risk nulliparous women (as defined in trial objectives)
  - Age ≥18 and <40 years
  - Singleton pregnancy
  - No contraindications to induction of labour
  - Must agree to outpatient induction at 39 weeks
  - No medical issues in or outside of pregnancy
  - Must live within 30 minutes or 15km of the hospital and have transport to hospital at all times during induction period
  - A normal amniotic fluid index (AFI) at 39 weeks' gestation is between 8 cm and 20 cm
  - Biophysical Profile Score (BPS) is 8/8
  - Bishops score <6
- **Exclusion criteria**
  - Multiparous women
  - Women with uterine scar
  - Women with low lying placenta
  - Women with BMI > 35
  - Multiple gestation
  - Known fetal anomaly or fetal growth restriction or oligohydramnios
  - Known maternal health problem e.g. hypertensive disease, cardiac disease, renal disease, diabetes, pulmonary disease, hepatic disease
  - Women with no transport to hospital or women who live >30 minutes or >15km from the hospital
  - Patients who have difficulty understanding the required protocol and follow up instructions (e.g. language barriers)

- Women <39+0 or greater than 39+4 weeks' gestation
    - Gestational age will be based on initial dating scan between 7-14 weeks, which confirms gestational age by CRL.
- Any factor which is a contraindication to induction of labour
    - Contraindications to trial treatment include patients that fall into any of the following categories:
    - If labour has started.
    - If oxytocic drugs and/or other labour induction agents have been given.
    - When strong prolonged uterine contractions would be inappropriate such as in patients.
    - Who have had previous major uterine surgery,
    - e.g. Caesarean section, myomectomy o With cephalopelvic disproportion o With fetal malpresentation
    - With suspicion or evidence of non-reassuring fetal testing
    - Who have had previous major surgery (e.g. other than biopsies and cervical abrasion) or rupture of the uterine cervix
    - When there is current pelvic inflammatory disease, unless adequate prior treatment has been instituted.
    - When there is hypersensitivity to dinoprostone or to any of the excipients listed in the SmPC for Propess/Prostin
    - When there is placenta previa or unexplained vaginal bleeding during the current pregnancy.
    - In the evidence of any sign of infection, including genital tract infection

Statistical methodology

Simple comparisons of proportions of patients with successful and analysis: vaginal birth will be compared using one-sample and two-sample tests for proportions. Multiple testing of primary outcomes will be corrected by hypothesis testing at the 2.5% level. The primary analysis population for non-inferiority will be the per-protocol population, supported by an intention-to-treat analysis.

Schematic of Study Design:



9. Introduction

9.1 Background

Induction of labour (IOL) has become quite topical in recent years, with studies examining the role of IOL in accomplishing lower caesarean section rates, reduced neonatal morbidity and mortality rates, and improved maternal experience. These outcomes have been examined through RCTs, observational and qualitative studies amongst others.

There is a growing body of evidence to suggest that IOL at 39 weeks' gestation in otherwise uncomplicated (normal risk) nulliparous women decreases the primary caesarean section rate, is cost effective, does not result in increased perinatal adverse outcomes, and may decrease adverse outcomes.

What is not clear from the literature is the ideal method of achieving successful induction of labour in such patients, and if this could be a process that can be managed outside of the hospital setting in the normal risk nulliparous group, thus reducing resource utilisation and allowing overall better experiences within the cohort being induced.

The IND HOME trial aims to assess two popular methods of induction, both of which allow the patient to return home for 12 or 24 hours after initiation of IOL. The main issue with offering IOL to women at 39 weeks is that there is a paucity of space and beds that would be needed in the cervical ripening stage of IOL, meaning that we cannot feasibly offer this choice to women at present. The outcome is assessment of vaginal delivery by any means within a given time frame (36 hours in the 12 hour Dilapan-S® group and 48 hours in the 24 hour Dilapan-S® and Propess groups), assessing suitability of both methods as effective cervical ripening agents.

Bearing in mind the increasing caesarean delivery rates worldwide, the potential for any decrease in the primary caesarean section rate could result in significant decreases in maternal morbidity and mortality, were a safe and attainable protocol for cervical ripening and induction of labour to be found. The promise of an overall safer option for mother and baby, and ability to offer this to our target cohort of normal risk nulliparous women would be a huge advance in obstetric care. Finding a way in which to do this effectively at home is critical for our ability to offer IOL to women safely. It would also likely lead to an increase in satisfaction in terms of mothers, who can enjoy home comforts whilst this stage of cervical ripening is initiated.

9.2 Preclinical data

Preclinical studies have demonstrated that dinoprostone is a locally acting substance which is rapidly inactivated and thus it has no significant systemic toxicity. The hydrogel and polyester polymers are inert compounds with good local tolerability. Reproduction toxicity, genotoxic or

carcinogenic effects of the polymers have not been investigated but systemic exposure is negligible[i].

9.3 Clinical data

It is evident in recent research that induction at 39 weeks may result in lower adverse outcomes for both mother and baby. Chen et al[ii] found that in the multiparous woman, the risk of composite adverse neonatal outcome and composite adverse maternal outcome was lower at 39 weeks' than at 40 & 41 weeks' gestation. The ARRIVE trial[iii] showed that the caesarean delivery rate was lower in normal risk nulliparous women who underwent IOL at 39 weeks' gestation compared to expectant management, as well as lower rates of hypertension, but with no change in costs for the centre, and no change in adverse neonatal outcome.

In terms of outpatient IOL, a Cochrane review[iv] examined 4 published and unpublished randomized and quasi randomized trials with a combined total of 1,439 women. These trials assessed different methods of induction in the outpatient setting; thus, the results were not amalgamated. In those trials examined, vaginal PGE2 was used in two; and the outcomes showed no evidence of a difference in the women requiring instrumental delivery, with a similar rate of hospital stay in both groups. One study employed the use of a prostaglandin pessary in 300 women. There was no difference between groups for most review outcomes, including successful induction of labour. Mechanical induction with a Foley catheter was used in one study comprising 111 women. In this study there was no difference between groups.

A more recent Cochrane review in 2017[v] assessed outpatient vs inpatient induction for improving patient outcomes. This review included 34 RCTs comprising 11 different methods for labour induction with 5003 randomised women, where women received treatment at home or were sent home after initial treatment and monitoring in hospital. They concluded that outpatient IOL appears feasible and safe, but that in general there is insufficient evidence to detect differences. The review specifically suggested that there have been very few direct comparisons between different methods of labour induction in outpatient settings.

A Portuguese RCT[vi] examined the use of mechanical cervical priming with a Foley catheter in the outpatient vs inpatient setting, finding that outpatient priming was as safe and effective as inpatient priming, but with a shorter hospital stay, and less caesarean deliveries for failed induction. Recent studies have compared safety indices of balloon catheters with Dilapan-S® [vii] and found that DilapanS® is not inferior to the Foley balloon for cervical ripening at term. Overall advantages of Dilapan-S® included FDA approval, the absence of anything protruding from the vagina, favourable safety profile, and the lack of applying tension to a Foley catheter needed for use, as well as patient satisfaction.

A survey of outpatient IOL in the UK[viii] showed that 16.5% of hospitals within the UK already provide outpatient IOL for post-dates singleton normal risk pregnancies. Of those providing the service 84% were using Propess as the method of initiating labour, while others used dinoprostone gel

or isosorbide mononitrate. A further 1.2% were aiming to start an outpatient IOL service within the near future. Notably, at the time of the survey, no hospital was using mechanical dilators such as Dilapan-S® or an intracervical balloon.

A prospective pilot study was carried out by Crosby et al [ix]in the National Maternity Hospital, Dublin who examined Propess and Dilapan-S® for use for inpatient IOL in the post-dates setting. This was a single-centre, prospective, observational pilot study (non-blinded / non-randomized) in which 52 women received either Dilapan-S® or Propess for IOL. The study found that Dilapan-S® was an acceptable, safe form of induction of labour in post-dates uncomplicated nulliparous pregnancy.

Following the ARRIVE trial, whereby women were induced at 39 weeks' gestation, the data would suggest that there was a decrease in frequency of caesarean delivery. It also noted that the incidence of hypertension was reduced. Overall the trial showed no difference in cost of healthcare in this cohort. It did not find any difference in primary perinatal outcome; however, the trial was notably not powered to assess this outcome and it was not a primary endpoint. In terms of outpatient vs inpatient protocols, the best available evidence appears to show no difference in safety data between inpatient and outpatient induction.

Some studies have examined the overall experience of outpatient induction from the maternal perspective through qualitative methods [x] and have found that in general, women liked the opportunity to remain at home, and felt the home setting offered freedom, security and reassurance compared to the hospital, which was viewed as constraining.

Overall, evidence points towards outpatient induction of labour as being safe, effective and well received by women. Furthermore, evidence for inpatient and outpatient induction of labour by mechanical methods such as Dilapan-S® shows it to be safe and effective as a cervical ripening agent. Propess is a well-established method of induction in both inpatient and outpatient settings and is widely used within Ireland and the UK.

9.4 Rationale and risks/benefits

The rationale of this study is to investigate methods (Propess vs Dilapan-S®) of outpatient-based induction of labour at 39 weeks in normal risk nulliparous women.

Currently the Rotunda is the only known hospital in Ireland performing outpatient IOL. This is offered to normal risk nulliparous and multiparous women when their induction process begins with Propess for uncomplicated post-dates (i.e. 41+3/41+5 as per hospital protocol) induction.

This study will recruit women as per the inclusion and exclusion criteria as above, and a date for IOL will be set for between 39+0 and 39+4 weeks gestation. The assessments will take place in an assigned ward, where the patient will have fetal monitoring and maternal monitoring (CTG and

recording of vitals, respectively) and a study investigator will assess the patient and begin one of two methods based on the randomization to one of two groups.

This study will aim to assess if Propess and Dilapan-S® have any major differences failing to achieve a vaginal delivery within a given time frame, as described above. It will also assess if there is any difference in efficacy in terms of timing of Dilapan-S® (i.e. Dilapan-S® for 12 hours vs 24 hours). If Dilapan-S® is shown to be non-inferior, it would allow us to adapt practice in order to introduce this method for outpatient IOL, improve the process and allow for safe and effective methods of outpatient IOL. It may also be the basis of new guidelines for induction of labour nationally. In previous years, prostaglandin gel would have been the main form of hormonal cervical ripening, and Foley catheters or laminaria used as mechanical. However, Propess has been extremely popular due to its reduction in necessary vaginal examinations (prostaglandin gel required reassessment every 6 hours vs Propess every 24 hours); and the ability to remove Propess if any side effects occur. Propess is now commonly used as the induction method of choice in many women for these reasons. A Foley catheter has been used in order to provide a mechanical induction method for those in whom hormonal methods are contraindicated. However, this necessitated taping the catheter to the patient's leg in order to keep pressure, which is not to the liking of many patients. Laminaria were originally made from the dried stems of laminaria seaweed, which was a biological material and so had the side effect of potential reactions to this.

Both methods of IOL will be used as intended within their license. There will be no changes to suggested timing or delivery of either device- i.e. Propess (1 delivery system) will be inserted and the patient allowed to return home before removal by 24 hours. Dilapan-S® (the required number of rods as per manufacturer guidelines) will be inserted and the patient allowed to return home before removal by either 12 hours or 24 hours.

9.5 Assessment and management of risk

Induction of labour is a widely studied area. Initially and currently most centres will offer IOL to postdates (i.e. 40+ weeks gestation) in accordance with their local guidelines in order to decrease risks of stillbirth, the incidence of which increases sharply after 42 weeks' gestation. However, IOL has routinely been offered earlier due to maternal age, suspected macrosomia, hypertensive disorders of pregnancy, and medical issues in the mother or baby. In general, IOL between 41-42 weeks has been shown to reduce the risk of caesarean section compared to expectant management, and recently the ARRIVE trial has shown that IOL at 39 weeks resulted in a further decrease in CS rate by 4% if IOL took place at 39 weeks[iii].

Therefore, we know that generally, IOL is a safe endeavour, and appears to be safer still at 39 weeks. A further study published in August 2019 showed similar findings in multiparous women, showing decreased perinatal morbidity without an increase in caesarean delivery rate in the IOL at 39 weeks group in comparison to expectant management[xi]. The maternal complications of prolonged pregnancy are linked closely with the risks of labour dystocia, genital tract trauma, CS, PPH and anxiety[xii].

As described above, outpatient IOL has been described as safe in multiple studies and a Cochrane review, but lacks evidence on efficacy. Therefore this study aims to provide further high quality evidence on rates of vaginal delivery after outpatient IOL at 39 weeks' gestation compared to published inpatient rates at 39 weeks gestation.

9.6 Potential Risks

Propess:

Risks of hyperstimulation with Propess have been reported as between 0-5% in various studies. Hyperstimulation can be treated with antitocolytics such as terbutaline if there are signs of nonreassuring fetal testing, as per standard practice. An advantage of using Propess over prostaglandin gel preparations is that once removed, dinoprostone in this form has a half-life of 1-3 minutes[i], meaning that hyperstimulation that is reported with Propess is often resolved by removal of the pessary alone. With respect to outpatient IOL, patients are instructed to return to the hospital if they are experiencing persistent abdominal pain or increased frequency of contractions suggestive of hyperstimulation.

Risks of Propess as per SmPC:

The most commonly reported adverse drug reactions in placebo-controlled and active comparator efficacy clinical trials (N=1116) were "fetal heart rate disorder" (6.9%), "uterine contractions abnormal" (6.2%) and "abnormal labour affecting foetus" (2.6 %).

The table below displays the main ADRs distributed by system organ classes (SOC) and frequency. Further, the ADRs seen during post-marketing experience are mentioned with unknown frequency.

System organ class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Not known: (cannot be estimated from the available data)**
Blood and lymphatic system disorders			Disseminated intravascular coagulation
Immune system disorders			Anaphylactic reaction Hypersensitivity
Nervous system disorders		Headache	

Cardiac disorders	Fetal heart rate disorder [1]*		
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders		Neonatal respiratory distress related conditions	
Gastrointestinal disorders			Abdominal pain, Nausea, vomiting, diarrhoea
Hepatobiliary disorders		Neonatal hyperbilirubinaemia	
Skin and subcutaneous tissue disorders		Pruritus	
Pregnancy, puerperium and perinatal conditions	Abnormal labour affecting foetus [2]* Uterine contractions abnormal [4]* Meconium in amniotic fluid	Postpartum haemorrhage, Premature separation of placenta, Apgar score low Arrested labour Chorioamnionitis Uterine atony	Anaphylactoid syndrome of pregnancy Fetal distress syndrome [3]*
Reproductive system and breast disorders		Vulvovaginal burning sensation	Genital oedema
General disorders and administration site conditions		Febrile disorders	
Injury, poisoning and procedural complications			Uterine rupture

Adverse reactions observed in clinical studies are presented according to their incidence, post authorisation reported adverse reactions are presented in the column frequency unknown.

1* "Fetal heart rate disorder" was in clinical studies reported as "fetal heart rate abnormalities", "fetal bradycardia", "fetal tachycardia", "unexplained absence of normal variability", "fetal heart rate decreased", "fetal heart rate deceleration", "early or late decelerations", "variable decelerations", "prolonged decelerations".

2* “Abnormal labour affecting foetus” as expression for hyperstimulation syndrome was in clinical studies reported as “uterine tachysystole” combined with “late decelerations”, “fetal bradycardia”, or “prolonged decelerations ”

3* “Fetal distress syndrome” was also reported as “fetal acidosis” , “pathological CTG”, “fetal heart rate abnormalities”, “intrauterine hypoxia” or “threatening asphyxia”. The term itself is unspecific, has a low positive predictive value and is often associated with an infant who is in good condition at birth.

4* “Uterine contractions abnormal” were reported as “uterine hyperstimulation” and “uterine hypertonus”.

Dilapan-S®:

Risks of hyperstimulation with Dilapan-S® have been reported as ‘very low’. At the time of writing, there was one case of hyperstimulation with Dilapan-S® reported in the e-registry, with no established causality.

The methods used in this study are used as per manufacturer and licencing guidelines, and therefore equate to the overall risk of use, with no theoretical higher risk than in the general population.

Potential risks of Dilapan-S® include: (as quoted by manufacturer information)

- Device entrapment and/or fragmentation or detachment of the handle
- Device expulsion
- Device retraction into the uterus
- Discomfort or bleeding during and/or after insertion
- Spontaneous rupture of membranes
- Spontaneous onset of labour
- Injury to the birth canal (cervical laceration) Advice from information leaflet for Dilapan-S®
- The patient should be advised to report any excessive bleeding, pain, or increase in temperature.
- The patient should avoid bathing, douching and refrain from sexual intercourse while DilapanS® is in place.

Side effects:

- The patient may experience a so called “vaso-vagal reaction” also known as “faintness”. This temporary status of weakness, paleness, nausea, dizziness or loss of consciousness may be caused by cervical manipulation. By remaining recumbent for 3 to 10 minutes these symptoms usually disappear.

The methods used in this study are used as per manufacturer and licencing guidelines, and therefore equate to the overall risk of use, with no theoretical higher risk than in the general population.

9.7 Potential Benefits

The benefits are that induction at this stage may decrease the risk of having a caesarean section. It may also decrease the risk of complications for mothers and babies.

Being induced at 39 weeks may also allow for delivery before complications occur later in the pregnancy. For example, meconium stained liquor is more common after 40 weeks of gestation. There is a decreased risk of shoulder dystocia, a decreased risk of OASI, and a decreased risk of PPH. There is a decreased risk of NICU admission for various reasons as detailed in the literature review above.

This study may help formulate an effective plan for induction of labour in many women in the comfort of their own homes in the future, benefiting a multitude of future patients.

Additionally, there are potential benefits to maternity services including a reduction in length of antenatal stay in hospital, less strain on maternity units / resources, a potential reduction in financial costs and avoidance of unnecessary hospital admissions.

10 Objectives

10.1.1 Primary objective(s):

1. To demonstrate non-inferiority of efficacy for Dilapan-S® (12 hours or 24 hours insertion) to Propess for outpatient induction of labour at 39 weeks' gestation in otherwise uncomplicated, normal risk* nulliparous women.

2. To demonstrate non-inferiority of efficacy for Dilapan-S® 12-hour insertion to Dilapan-S® 24hour insertion for outpatient induction at 39 weeks' gestation in otherwise uncomplicated, normal risk nulliparous women.

* A pregnancy is considered "normal-risk" when there are no active complications and there are no maternal or fetal factors that place the pregnancy at increased risk for complications. Specifically, the following conditions should be met to consider a pregnancy to be normal risk:

- Singleton pregnancy
- Cephalic presentation
- Term gestation (37-42 weeks gestational age)
- Maternal pre-pregnancy body mass index < 35kg/m2
- Maternal age of ≥ 18 and < 40 years •
- No evidence of the following conditions:
    - Pre-pregnancy diabetes
    - Gestational diabetes
    - Pre-pregnancy hypertension
    - History of preterm birth
    - History of prior poor pregnancy outcome
    - History of a prior caesarean delivery
    - Cervical cerclage in situ
    - Premature rupture of membranes
    - Congenital fetal anomalies

10.1 Secondary Objective(s)

1. To demonstrate non-inferiority of efficacy for outpatient induction at 39 weeks gestation in the study to published inpatient induction rates.

2. To compare the secondary outcomes measures between the study treatment arms.

10.2 Study Outcome Measures

For all study participants, information will be recorded in the electronic chart as is standard for all patients in the hospital. Data on all of the above primary and secondary objectives will be collected and collated.

At the initiation of induction, the gestational age and exact time of initiation of induction will be recorded.

A questionnaire will be given to participants to complete during their postnatal admission in the first feasible instance following delivery in order to assess their satisfaction scores with the process of outpatient induction.

10.2.1 Primary outcome measure

The primary outcome measure (efficacy measure) is failure to achieve vaginal delivery (or, equivalently, operative vaginal delivery or SVD) within 36 hours (12 hour Dilapan-S® group) or 48 hours (24 hour Dilapan-S® /Propess groups) from commencement of induction. This will allow assessment of effective methods of IOL in the outpatient setting. The window for induction will be 39+0 to 39+4 weeks gestation.

10.2.2 Secondary outcome measures

1. Overall change in Bishop score before and after cervical ripening
2. Rates of vaginal delivery at 36 hours after insertion of either Propess or Dilapan-S®
3. Rates of vaginal delivery at 24 hours after insertion of either Propess or Dilapan-S®
4. The need for second induction modality
5. Rates of hyper-stimulation
6. Rate of failed induction
7. Overall length of stay in hospital
8. Rates of adverse neonatal outcome
9. Rates of adverse maternal outcomes
10. Maternal satisfaction scores with the outpatient induction process
11. Caesarean delivery rates, categorized by “overall rate”, “rate for failure to progress/failed induction”, and “rate for non-reassuring fetal testing”
12. Analgesia use in each group, including rates of epidural
13. Compare rates of 39 weeks’ successful vaginal delivery in the outpatient setting to published rates of successful vaginal delivery in the inpatient setting.

The primary objectives will therefore assess the efficacy of achieving labour with each of the study induction methods. The secondary objectives will assess safety measures and maternal

satisfaction scores which are important factors in deciding whether this is a feasible option long term, and risk stratification in this process. Although many studies have shown both induction mediums to be low risk, it is important to compare the outcomes as above in order to guide the best possible IOL methods and create the most appropriate protocol for women to undergo IOL.

11 Trial design

11.1 Overall design

This study is an open-label parallel group single centre trial.

Participants are normal risk nulliparous women who have no pregnancy-related or medical contraindication to IOL. Women will be randomized to one of three induction groups- Dilapan-S® (12hour insertion or 24-hour insertion) or Propess, which will be initiated between 39+0 and 39+4 weeks' and then allowed to return home for either 12 or 24 hours. They will be readmitted 12/24 hours later and reassessed in order to continue with induction of labour.

Patient recruitment will take place over 24 months within a single centre. The study will recruit a maximum 155 women for each study arm. Total duration of participants involvement in the trial will be 8 weeks to allow for postpartum follow up.

The protocol and visit specifics are detailed below in section 14.4, 14.5 and 14.6.

12 Selection of Subjects

This trial will be coordinated from the Rotunda Hospital, the Chief Investigator site. Identification of potential subjects will be from the antenatal clinic lists. Potential participants who may wish to enquire about the study through advertising will also be able to contact the investigator. The expected number of participants that will be available for screening over 24 months is approximately 6000, with a sample size of 465 to be recruited.

12.1 Inclusion criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Provide signed and dated informed consent form
- Willing to comply with all study procedures and be available for the duration of the study
- Normal risk nulliparous women (as defined in trial objectives)
- Age ≥18 and <40 years
- Singleton pregnancy
- No contraindications to induction of labour
- Must agree to outpatient induction at 39 weeks
- No medical issues in or outside of pregnancy
- Must live within 30 minutes or 15km of hospital and have transport to hospital at all times during induction period
- A normal amniotic fluid index (AFI) at 39 weeks' gestation is between 8 cm and 20 cm

- Biophysical Profile Score (BPS) is 8/8
- Bishops score <6

12.2 Exclusion criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Multiparous women
- Women with uterine scar
- Women with low lying placenta
- Women with BMI > 35
- Multiple gestation
- Known fetal anomaly or fetal growth restriction or oligohydramnios
- Known maternal health problem e.g. Hypertensive disease, cardiac disease, renal disease, diabetes, pulmonary disease, hepatic disease
- Women with no transport to hospital or women who live >30 minutes or >15km from the hospital
- Patients who have difficulty understanding the required protocol and follow up instructions (e.g. language barriers)
- Women <39+0 or greater than 39+4 weeks' gestation ○ Gestational age will be based on initial dating scan between 7-14 weeks, which confirms gestational age by CRL.
- Any factor which is a contraindication to induction of labour
- Contraindications to trial treatment include patients that fall into any of the following categories:
    - If labour has started.
    - If oxytocic drugs and/or other labour induction agents have being given.
    - When strong prolonged uterine contractions would be inappropriate such as in patients who have had previous major uterine surgery, e.g. Caesarean section, myomectomy
    - With cephalopelvic disproportion
    - With fetal malpresentation
    - With suspicion or evidence of non-reassuring fetal testing
    - Who have had previous major surgery (e.g. Other than biopsies and cervical abrasion) or rupture of the uterine cervix
    - When there is current pelvic inflammatory disease, unless adequate prior treatment has been instituted. ○ When there is hypersensitivity to dinoprostone or to any of the excipients listed in the SmPC for Propess/Prostin
    - When there is placenta previa or unexplained vaginal bleeding during the current pregnancy.
    - In the evidence of any sign of infection, including genital tract infection

13 Recruitment

A total 465 normal risk nulliparous women will be recruited from the antenatal clinics in the hospital provided they fit inclusion criteria. There are approximately 3000 nulliparous women per annum attending the Rotunda Hospital who deliver at full term through any means. Breech presentation is present in approximately 160 cases within this, giving an average pool of 2840 singleton cephalic nulliparous women to recruit from per year.

The study will be advertised through posters and media in the antenatal clinic waiting areas. The study may be advertised via the hospital website and social media pages. Additionally, medical staff will be aware of potential recruitment criteria and will be able to refer to study investigators if patients show an interest in taking part in the study. Patients who are eligible may be identified from the clinic lists via e-chart/iPIMS and contacted to assess interest if eligible.

13.1 Onsite Patient Contact Log

A patient screening log and patient enrolment log will be maintained at the trial centre. The screening log will detail the patient's full name, date of birth, hospital number and contact details for consented and screened patients. This log will be maintained locally and will not be sent outside the trial centre but may be monitored by authorised onsite personnel.

13.2 Screening Procedure

Participants will be identified from the antenatal clinic lists at the maternity site. A screening log will be maintained at each site for the purposes of monitoring eligibility and participation rates at each site. Eligible women who consent to trial participation will have their details entered onto the Patient Enrolment Log which will identify the patients by a unique identification number.

Patient Information Leaflets will be issued to potential participants in the antenatal clinics. Monthly recruitment data, to include number of women eligible and number recruited, will be communicated to the Project Manager and will be reviewed together with the Principal Investigator and TSC.

Potentially eligible participants will be approached by the investigator between 34-38 weeks' gestation, and will be given the patient information leaflet regarding the study. If interested they will then be invited to a consultation with a member of the research team at a dedicated antenatal clinic between 38+0 and 39+0 weeks' gestation. The study will be described, supplemented by written information, and eligible women will be invited to participate. Sufficient time for reflection will be allowed before written informed consent is obtained by the

investigator. At this screening visit, a medical history will be recorded, and notes reviewed to ensure that the patient fulfils the inclusion criteria for study participation and that no exclusion criteria are met prior to randomisation.

14 Study procedures and schedule of assessments

14.1 Informed consent procedure

It is the responsibility of the Principal Investigator at the recruitment site, or another investigator delegated by the Principal Investigator to obtain written informed consent from each subject prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. “Adequate time” must be given for consideration by the patient before taking part.

The Investigator or designee will explain that patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason for withdrawal. No clinical trial procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into the trial.

A copy of the signed Informed Consent Form will be given to the participant. The original signed form will be retained in the Investigator Site File (ISF) at the study site and a copy placed in the medical notes.

If new safety information results in significant changes in the risk/benefit assessment, the patient information leaflet will be reviewed and updated if necessary and subjects will be provided with the new PIL in a timely manner and new consent obtained.

14.2 Randomisation procedures

A computer-generated randomisation sheet will be used to assign study participants to either Propess, Dilapan-S® 12 hours or Dilapan-S® 24 hours groups at Visit 1. The randomization sheet will provide notification of the treatment package to be assigned to the participant and a log of each randomisation will be retained. The randomisation will be performed by the study investigator providing the treatment. Subsequent to screening and consent procedures, the participants will be randomized to one of the three groups. The randomization will use a block size of 4 and the random number seedgenerator and generating program will be retained for re-producibility. The software SAS 9.4 will be used to generate the randomization list.

14.3 Unblinding

Not applicable as this trial is open label.

14.4 Trial Visit Overview

a. Approach of potentially eligible participants will occur between 34+0 and 39+0) at which point the PIL will be distributed to interested parties.

b. Dedicated clinic visit ('Visit 1': Consent and screening) will occur between 38 and 39 weeks. Patients will be screened for inclusion and exclusion criteria and will be offered to participate in the study. Informed consent will be obtained at this point in time, and a date & instructions for visit 2 given. Randomization will occur at this visit.

c. Visit 2 will occur between 39+0 and 39+4 and IOL will be commenced.

d. Visit 3 will occur within 11-28 hours of Visit 2.

e. Visit 4 (between 12 hours and 5 days of delivery), will be referred to as 'Delivery Visit'.

f. Visit 5 follow up will be conducted at 6 weeks post-partum (+/- 7 days)

14.5 Schedule of visits

2. Visit #	**1**	**2**	**3**	**4**	**5**
Visit Type	Screening & consent, Randomisation	Induction visit	Re-assessment Visit	Delivery Visit	Follow-up visit (or phone call)
Visit Timing	Between 38+0 & 39+0 weeks gestation	Between 39+0 and 39+4 weeks gestation	Within 11-28 hours of Visit 2	Between 12 hours and 5 days of delivery date	6 weeks Postpartum (+/- 7 days
Informed Consent	X				
<u>Screening Procedures</u>					
Obtain relevant medical history *(including medication history)*	X				
Vital Signs *(include BP, Pulse, temperature, RR, O2 sats)*	X	X	X	X	
Urinalysis	X	X			
Bishop's Score		X	X		
Weight, Height and BMI	X[1]				

Ultrasound	X	X			
Physical examination *(only if symptom driven)*	X	X	X	X	
Abdominal examination	X	X	X		
Eligibility determination *(inclusion/exclusion assessment)*	X	X2			
Randomisation	X				
IMP administration		X3			
Participant safety checklist		X[4]			
Delivery details				X	
Maternal Satisfaction Questionnaire				X	X5
Neonatal outcomes[6]				X	X
Adverse Events review		X	X	X	X
Concomitant Medication review	X	X	X	X	X

1. ***If not already documented in the medical chart***
2. ***If Visit 1 & Visit 2 are not conducted on the same day, eligibility must be re-assessed***
3. ***After IMP is inserted, there will be a further CTG for 60 mins to ensure there are no signs of non-reassuring fetal testing before allowing the patient to return home. Patients will receive telephone calls from healthcare staff at approximately 8 hours and 14 hours post administration of IMP (Propess or Dilapan) to assess for maternal and fetal well-being***

4. ***Patients will be given a safety checklist prior to discharge home, and will be instructed to complete this checklist every 2 hours while at home. The checklist will include documenting the presence / absence of pains, fetal movements, rupture of membranes and vaginal bleeding every 2 hours. Patients will be given strict guidance on when to remove the Propess (if randomised to this arm), when to return to the hospital, including Instructions to return to the hospital in the event of spontaneous rupture of membranes, regular painful uterine contractions, increased frequency of uterine contractions, reduced fetal movements or vaginal bleeding (this will be outlined in the Patient Information Leaflet)***

5. ***Questionnaire will be posted to participants who did not receive it at Visit 4***

6. ***Birthweight & birthweight centile, apgar score at 1 minute, apgar score at 5 minutes, meconium staining noted, metabolic acidosis (defined as cord-artery pH < 7.05 with base deficit ≥ 12mmol/l), antibiotic use for neonatal infection, admission to neonatal unit, length of stay in neonatal unit, neonatal mortality***

14.6 Baseline assessments

Baseline assessments at recruitment include:

- Obtain medical history
- Vital signs
- Physical examination (if symptom driven)
- Abdominal examination
- Weight, height, BMI
- Urinalysis
- Ultrasound
- Randomisation

Visit 2 assessments will include:

- Vital Signs
- Urinalysis
- Bishop's score
- Ultrasound
- Physical examination (if symptom driven)
- Abdominal examination
- IMP administration
- Adverse event review
- Concomitant medication review
- CTG

Visit 3 assessments will include:

- Vital Signs
- Bishop's score
- Physical examination (if symptom driven)
- Abdominal examination
- Adverse event review
- Concomitant medication review
- CTG

Visit 4 assessments will include:

- Vital Signs
- Physical examination (if symptom driven)
- Delivery details
- Maternal Satisfaction Questionnaire
- Neonatal outcomes
- Adverse event review
- Concomitant medication review

Visit 5 assessments will include:

- Maternal Satisfaction Questionnaire *(if unable to complete at Visit 4)*
- Neonatal outcomes
- Adverse event review
- Concomitant medication review

14.7 Treatment procedures

Propess will be administered vaginally at a standard dosing protocol, i.e. 1 device containing 10mg dinoprostone over 24 hours.

Dilapan-S® will be administered at a standard dosing protocol, i.e. the required number of rods intracervically over 24 hours.

Prostaglandin E2 will be administered if required at one 1mg dose vaginally 24 hours after the induction method has been inserted, at the discretion of the examining physician.

14.8 Subsequent assessments

N/A

14.9 Flowchart of study assessments

Assessment table of all procedures/tests/IMP administration will be completed at each visit.

14.10 Methods

14.10.1 Laboratory procedures

N/A

14.11 Definition of end of trial

The end of the trial will be defined as the 6 week post-partum consultation.

14.12 Discontinuation/withdrawal of participants and 'stopping rules'

Participants will be withdrawn from the trial if:

- There is evidence of any complications of pregnancy (e.g. PET) that deems the patient unsuitable for outpatient management.
- If it is deemed unsafe to allow the participant to return home once the IOL has commenced.
- Recording of any withdrawals will take place including the reason for withdrawal and the circumstances around the withdrawal.
- The trial will be stopped if there are any concerns for patient safety.

15 Name and description of all drugs or devices used in the trial

Propess Dinoprostone 10mg vaginal delivery system. The insert contains 10mg dinoprostone which is released over 24 hours.

Dilapan-S® is an osmotic hygroscopic dilator produced from a patented Aquacryl hydrogel.
Prostin is an intravaginal gel containing prostaglandin E2.

15.1 Treatment of subjects

Investigational product/treatment

Propess will be administered vaginally at a standard dosing protocol, i.e. 1 device containing 10mg dinoprostone over 24 hours. This is the standard dose for Propess as per manufacturer guideline and licencing.

Dilapan-S will be administered at a standard dosing protocol, i.e. the required number of rods intracervically over 12 hours or 24 hours as per manufacturer guideline and licencing.

15.2 Concomitant medication

There are no specific concomitant medications that will restrict usage of these medications in this cohort of normal risk nulliparous women with no medical comorbidities requiring long term medications except for the use of herbal medications which might affect uterine contractions. However, if a patient is being treated for a medical condition such as essential hypertension/epilepsy/diabetes/moderate-severe asthma, and requiring any concomitant medications, this would be subject to our exclusion criteria as above, thus making the patient ineligible for the trial. Concomitant medications will be captured from Visit 2 until the 6 week postpartum follow up.

16 Investigational Medicinal Product

According to the definition of the EU clinical trial directive 2001/20/EC, an investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation, but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

16.1 Name and description of investigational medicinal product(s)

Name of the medication: PROPESS 10mg vaginal delivery system

Qualitative and quantitative composition: Each vaginal delivery system consists of a nonbiodegradable polymeric drug delivery device containing 10mg dinoprostone (Prostaglandin E2) dispersed throughout its matrix

Pharmaceutical form: Vaginal delivery system

PROPESS is presented as a thin, flat semi-transparent polymeric vaginal delivery system which is rectangular in shape with rounded corners contained within a knitted polyester retrieval system.

Name of the medication: Dilapan-S®

Qualitative and quantitative composition is an osmotic hygroscopic dilator manufactured from an anisotropic xerogel of **Aquacryl®**, and comes in sterile, single use rods.

Pharmaceutical form: Dilapan-S® Dilapan-S® is classified as a CE marked medical device and contains no active pharmacological substance.

16.2 Name and description of each NIMP

Name of the medication: Prostin E2 Vaginal Gel 1 mg.

Qualitative and quantitative composition: Each 3 g gel (2.5 ml) syringe contains 1 mg dinoprostone.

Pharmaceutical form: Vaginal gel. Semi-translucent, thixotropic gel.

Prostin is being administered within its therapeutic indication as appropriate. It is not considered to be an investigational medicinal product for the purpose of this trial. At Visit 3, the

administration of the Non-IMP Prostin (if necessary) will be captured in the participant medical record and this data will be used to inform the secondary outcome measure.

16.3 Summary of findings from non-clinical studies

The following are available from the SmPC forms for the relevant medications.

Propess 10mg vaginal delivery system

Preclinical studies have demonstrated that dinoprostone is a locally acting substance which is rapidly inactivated and thus it has no significant systemic toxicity.

The hydrogel and polyester polymers are inert compounds with good local tolerability.

Reproduction toxicity, genotoxic or carcinogenic effects of the polymers have not been investigated but systemic exposure is negligible.

16.4 Summary of findings from clinical studies

Overall, throughout the last years, all methods have been studied widely and have been repeatedly deemed safe methods of IOL. Known and acknowledged risks of both prostaglandin-based devices include the risk of uterine hyperstimulation with the potential to cause fetal heart rate abnormalities. Propess is a removable method, and studies have reported hyperstimulation can resolve with removal of the device.

Propess has been widely used, and thus the subject of many clinical trials in terms of efficacy and safety. Shirley (2018) published a review which outlines the efficacy and safety of the dinoprostone vaginal insert.

In terms of efficacy, studies as far back as 1992 have shown prostaglandin pessaries to be effective methods of cervical ripening[xiii],[xiv]. Risks of uterine tachysystole are acknowledged but multiple studies have shown reversal of this complication with removal of the pessary within 2-15 minutes. Tekin et al published a study in 2015 showing that Labour induction with Propess(®) is safe during both midwifeled and obstetrician-led labour management[xv].

In terms of outpatient IOL, a Cochrane review[iv] examined 4 published and unpublished randomized and quasi randomized trials with a combined total of 1,439 women. These trials assessed different methods of induction in the outpatient setting; thus, the results were not amalgamated. In those trials examined, vaginal PGE2 was used in two; and the outcomes showed no evidence of a difference in the women requiring instrumental delivery, with a similar rate of hospital stay in both groups. One study employed the use of a prostaglandin pessary in 300 women. There was no difference between groups for most review outcomes,

including successful induction of labour. Mechanical induction with a Foley catheter was used in one study comprising 111 women. In this study there was no difference between groups.

Dilapan-S®

A prospective pilot study was carried out by Crosby et al[ix] in the National Maternity Hospital, Dublin who examined Propess and Dilapan-S® for use for inpatient IOL in the post-dates setting. This was a single-centre, prospective, observational pilot study (non-blinded / non-randomized) in which 52 women received either Dilapan-S® or Propess for IOL. The study found that Dilapan-S® was an acceptable, safe form of induction of labour in post-dates uncomplicated nulliparous pregnancy.

Recent studies have compared safety indices of balloon catheters with Dilapan-S® [vii] and found that

Dilapan-S® is not inferior to the Foley Balloon for cervical ripening at term. Overall advantages of Dilapan-S® included FDA approval, the absence of anything protruding from the vagina, favourable safety profile, and the lack of applying tension to a Foley catheter needed for use, as well as patient satisfaction.

16.5 Summary of known and potential risks and benefits

As evidenced in the literature review, benefits of induction of labour include a reduced caesarean section rates, and a reduced maternal and neonatal morbidity rate. The specific stated risks of each modality involved in this study are stated below.

<u>Propess 10mg vaginal delivery system</u>

Benefits of Propess over other induction methods include:

Reduction in frequency of vaginal examinations

Undesirable effects as per IMP SmPC

Summary of safety profile:

The most commonly reported adverse drug reactions in placebo-controlled and active comparator efficacy clinical trials (N=1116) were “fetal heart rate disorder” (6.9%), “uterine contractions abnormal” (6.2%) and “abnormal labour affecting foetus” (2.6 %).

The table below displays the main ADRs distributed by system organ classes (SOC) and frequency. Further, the ADRs seen during post-marketing experience are mentioned with unknown frequency.

Adverse reactions observed in clinical studies are presented according to their incidence, post authorisation reported adverse reactions are presented in the column frequency unknown.

System organ class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)	Not known: (cannot be estimated from the available data)
Blood and lymphatic system disorders			Disseminated intravascular coagulation
Immune system disorders			Anaphylactic reaction Hypersensitivity
Nervous system disorders		Headache	
Cardiac disorders	Fetal heart rate disorder [1]*		
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders		Neonatal respiratory distress related conditions	
Gastrointestinal disorders			Abdominal pain, Nausea, vomiting, diarrhoea
Hepatobiliary disorders		Neonatal hyperbilirubinaemia	
Skin and subcutaneous tissue disorders		Pruritus	
Pregnancy, puerperium and perinatal conditions	Abnormal labour affecting foetus [2]* Uterine contractions abnormal [4]* Meconium in amniotic fluid	Postpartum haemorrhage, Premature separation of placenta, Apgar score low Arrested labour Chorioamnionitis Uterine atony	Anaphylactoid syndrome of pregnancy Fetal distress syndrome [3]*

Reproductive system and breast disorders		Vulvovaginal burning sensation	Genital oedema
General disorders and administration site conditions		Febrile disorders	
Injury, poisoning and procedural complications			Uterine rupture

1* "Fetal heart rate disorder" was in clinical studies reported as "fetal heart rate abnormalities", "fetal bradycardia", "fetal tachycardia", "unexplained absence of normal variability", "fetal heart rate decreased", "fetal heart rate deceleration", "early or late decelerations", "variable decelerations", "prolonged decelerations".

2* "Abnormal labour affecting foetus" as expression for hyperstimulation syndrome was in clinical studies reported as "uterine tachysystole" combined with "late decelerations", "fetal bradycardia", or "prolonged decelerations "

3* "Fetal distress syndrome" was also reported as "fetal acidosis" , "pathological CTG", "fetal heart rate abnormalities", "intrauterine hypoxia" or "threatening asphyxia". The term itself is unspecific, has a low positive predictive value and is often associated with an infant who is in good condition at birth.

4* "Uterine contractions abnormal" were reported as "uterine hyperstimulation" and "uterine hypertonus".

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard.

Dilapan-S®

The possible benefits of using Dilapan-S® over the current (mechanical and pharmacological) methods of induction include the following:

- Significant increase in cervical ripening and Bishop Score, which allows for the initiation of labour induction
- Minimal risk of uterine hyper-stimulation and impact on the fetal heart rate
- Effective and safe for women who have had a previous caesarean section
- No pharmacological side effects

- Gradual and predictable dilation due to its mode of action
- High maternal acceptability
- Accentuates the physiological processes of labour
- Efficiencies in midwifery care due to its one-time application (PGs usually require multiple administrations)
- Patented hydrogel ensures higher efficacy and predictability of effect in comparison to natural seaweed laminaria tents with less potential for reactivity or allergy.
- Certified production and non-porous synthetic material ensure higher safety in comparison to laminaria tents
- Easy application and storage in room temperature
- Sterile nature by design

Potential risks of using Dilapan-S® are:

- Rupture of membranes
- Vaginal bleeding from cervix, usually from the time of insertion as there can be trauma to the cervical tissue during the insertion process
- Allergic reaction from hypersensitivity to the components
- Contamination of the device during insertion
- Cervical laceration
- Vaso-vagal reaction from manipulation of the cervix
- Entrapment of the device
- Fragments of the device in the genital tract
- Retraction of the device into the uterine cavity

16.6 Description and justification of route of administration and dosage

Propess Administration:

A cardiotocograph tracing will be completed for 20 minutes prior to insertion of Propess®. A vaginal examination to determine the Bishop's score will be completed. Propess® will be administered using the standard dosing protocol, i.e. one device containing 10mg dinoprostone, releasing 0.3mg per hour over 24 hours as as per the manufacturer's guidelines in the SmPC as follows:

- Propess® should be removed from the freezer just prior to the insertion
- No thawing is required prior to use
- There is a “tear mark” on the side of the foil sachet
- Open the package along the tear mark across the top of the sachet
- Do not use scissors or other sharp objects which may cut the retrieval system
- Propess® should then be inserted high into the posterior vaginal fornix using only small amounts of water-soluble lubricants to aid insertion
- After Propess® has been inserted, the withdrawal tape may be cut with scissors always ensuring there is sufficient tape outside the vagina to allow removal
- No attempt should be made to tuck the end of the tape into the vagina as this may make retrieval more difficult
- The patient should be recumbent for 20 to 30 minutes after insertion

The patient will remain in the outpatient department for one hour post insertion to monitor for any side effects or uterine contractions, during which time 60 minutes of cardiotocograph tracing will be performed. If cardiotocograph testing is reassuring the patient will be allowed home. A safety checklist will be given to each patient to complete every 2 hours while at home. The patient will be advised upon leaving the hospital to return if she experiences any of the following:

- Spontaneous rupture of membranes
- Reduced fetal movements
- Constant abdominal pain
- Regular / painful uterine contractions
- Vaginal bleeding
- If the Propess® falls out

The patient will be contacted via telephone call by a healthcare professional to assess for maternal and fetal wellbeing mid-afternoon (4pm) and evening (10pm) while the patient remains at home, based on a presumed 8am insertion time. Patients will return to the hospital approximately 24 hours post insertion of Propess® for further evaluation of their labour progress. The vaginal delivery system should be removed after 24 hours irrespective of whether cervical ripening has been achieved. A dosing interval of at least 30 minutes is recommended for the sequential use of oxytocin following the removal of the vaginal delivery system.

Dilapan-S® administration:

A cardiotocograph will be completed for 20 minutes prior to insertion of Dilapan-S®. A vaginal examination to determine the Bishop's score will be completed. Dilapan-S®® will be administered at a standard dosing protocol, i.e. the required number of rods intracervically over either 12 or 24 hours.

Usually a set of 3–5 rods is required as per the manufacturer's guideline and licencing. Dilapan-S® rods will be administered as follows:

- A bivalve speculum should be inserted and the vagina and cervix should be prepared with an antiseptic solution
- Dilapan-S® should be removed from the package using a sterile technique
- The surface of Dilapan-S® can be lubricated using sterile water or saline prior to insertion
- Dilapan-S® should be inserted into the cervical canal gradually and without undue force
- It should traverse the external and internal cervical os
- Dilapan -S should not be inserted past the handle. The border of the knob/collar should rest at the external os
- More than one Dilapan-S® can be inserted into the cervical canal as deemed appropriate by the healthcare professional following clinical judgement of the risk / benefit ratio
- The patient should be recumbent for 20 minutes to 30 minutes after insertion

A cardiotocograph will be completed in the outpatient's setting for 20-40 minutes post- insertion of Dilapan-S®. If cardiotocograph testing is reassuring the patient will be allowed home. The patient will be advised upon leaving the hospital to return if she experiences any of the following:

- Spontaneous rupture of membranes
- Reduced fetal movements
- Constant abdominal pain
- Regular / painful uterine contractions
- Vaginal bleeding
- If the Dilapan-S® rods fall out

16.7 Dosages, dosage modifications and method of administration

There are no dose adjustments to the above regime.

Dilapan-S® will involve the insertion of the required number of rods as per the manufacturers instruction.

16.8 Preparation and labelling of Investigational Medicinal Product

Preparation and labelling of the investigational medicinal products should be completed in accordance with the Annex 13 guidelines.

16.9 Drug accountability

Master inventory logs of the IMP and the placebo will be held in each pharmacy site to allow for traceability of the IMP. Shipment records or delivery documents will be in the site pharmacy and recorded in the log. Each patient will have a dispensed and returned accountability log.

Drug accountability logs will be kept in the pharmacy file at each study site and will be signed off at the end of the trial.

After site visits by the study monitor, returned IMP will be destroyed according to the local hospital destruction policy.

16.10 Source of IMPs including placebo

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

- Propess
- Dilapan-S®

16.11 Dose modifications

There are no dose modifications or deviations from the above specifications for this study.

16.12 Assessment of compliance

Compliance with medication is not applicable as administration of both IMPs are performed within a clinical setting by the treating investigator.

16.13 Post-trial IMP arrangements

There will be no arrangements to provide the IMPs to trial participants post trial as this study is specific to IOL.

17 Recording and reporting of adverse events and reactions

17.1 Definitions

Term	Definition
Safety Definitions for Propess Events	
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
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. *This includes medication errors, uses outside of protocol (including misuse and abuse of product)*
Serious adverse event (SAE)	Any adverse event that: • results in death, • is life-threatening, • requires hospitalisation or prolongation of existing hospitalisation,
	• results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect • Important Medical Event*
**These events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered 'serious'*	
Serious Adverse Reaction (SAR)	Events that meet the criteria of an SAE and a causal relationship between the investigational medicinal product and the event cannot be ruled out
SUSAR	Suspected Unexpected Serious Adverse Reaction A serious adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out: (a) in the case of a product with a marketing authorization, in the summary of product characteristics for that product, (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.
Safety Definitions for Dilapan-S® Events	

Adverse Device Effect (ADE)	All untoward and unintended responses to the medical device. The phrase "responses to a medical device" means that a causal relationship between the device under investigation and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
Serious Adverse Device Effect (SADE)	A serious adverse device effect (SADE) is any untoward medical occurrence seen in a patient that can be attributed wholly or partly to the device which resulted in any of the characteristics or led to characteristics of a serious adverse event as outlined above. SADE is also any event that may have led to these consequences if suitable action had not been taken or intervention had not been made or if circumstances have been less opportune.

17.2 Safety Event Recording

All Adverse Events (AEs) occurring during the study observed by the investigator or reported by the subject will be recorded on the CRF, except for those events that meet the definition of a nonreportable event. All AEs will be recorded from Visit 2 until the 6 weeks postpartum follow up visit

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to the study medication, other suspect medication or device and action taken and outcome. Follow-up information should be provided as necessary. All AEs will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

If the investigator suspects that the subjects' disease has progressed faster due to the administration of the IMP, then he will record and report this as an unexpected adverse event. It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the subject's removal from treatment. A subject may also voluntarily withdraw from treatment due to what she perceives as an intolerable AE. If either of these occurs, the subject must undergo an end-of-study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

17.3 Assessments of AEs

Each AE will be assessed for the following criteria:

17.3.1 Severity

Category	Definition
Mild	The AE does not interfere with the volunteer's daily routine, and does not require intervention; it causes slight discomfort
Moderate	The AE interferes with some aspects of the volunteer's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	The AE results in alteration, discomfort or disability which is clearly damaging to health

17.3.2 Causality

Category	Definition
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 (e.g. 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 patient's clinical condition, other concomitant treatments).
Not related*	There is no evidence of any causal relationship.
Not Assessable*	Unable to assess on information available.
**only events suspected to be related to Propess or Dilapan-S will be captured*	

- The assessment of relationship of all events to the administration of Propess or Dilapan-S® is a clinical decision based on all available information at the time of the completion of the case report form. The following categories will be used to define the causality of events.

17.3.3 Expectedness

Category	Definition
Expected	An adverse event that is classed in nature as serious and which is consistent with the information about the IMP listed in the Investigator Brochure (or SmPC if Licensed IMP) **or clearly defined in this protocol.**
Unexpected	An adverse event that is classed in nature as serious and which is not consistent with the information about the IMP listed in the Investigator Brochure (or SmPC if Licensed IMP)

The reference document to be used by the Study Coordinator to assess expectedness of the event against the IMP. The reference documents are the SmPC for Propess and the Dilapan-S® excerption of instructions for use.

17.3.4 Seriousness

The Investigator should make an assessment of seriousness as defined in section 17.2.

Collection, recording and reporting of adverse events to the Study Coordinator (RCSI) will be completed according to the RCSI Expedited Safety Reporting SOP.

17.4 Procedures for reporting SAEs

All Serious Adverse Events (SAEs) will be reported to RCSI Pharmacovigilance, except for those events that meet the definition of a non-reportable event. The Principal Investigator (PI) or appropriate designee is responsible for capturing all SAEs on appropriate trial specific forms, and reporting to RCSI Pharmacovigilance (Pharmacovigilance@rcsi.ie) within 24 hours of first becoming aware of the event *(as per the RCSI SOP on Expedited Safety Reporting).*

As outlined in Section 17.3, SAEs will be collected from Visit 2 until the 6 weeks postpartum consultation and will be followed until resolution or until stabilized with sequelae.

The following are a list of non-reportable events that are considered to be pregnancy or induction related. These events will not be recorded as adverse events for the purpose of this trial:

- Hospitalisation for labour and delivery
- Pelvic girdle dysfunction
- Indigestion
- Fatigue
- Constipation
- Shortness of breath
- Urinary frequency/ nocturia
- Migraine and tension headache
- Nosebleeds and bleeding gums
- Varicose veins
- Haemorrhoids
- Back pain
- Palpitations
- Carpal tunnel syndrome
- Bilateral oedema of feet/legs/hands
- Fetal normal variants on ultrasound: Pyelectasis, choroid plexus cysts, echogenic intracardiac focus
- Due to breast feeding issues or need for emotional support
- Due to blood pressure control issues
- Due to shortness of breath
- Due to ante-partum haemorrhage
- Due to secondary post-partum haemorrhage
- Due to the need for IV antibiotics for a delivery related infection
- Due to concerns regarding baby including previously undiagnosed anomalies, weight gain or issues unrelated to labour and delivery.
- Any pre-existing anomaly in the baby that was previously undiagnosed but unrelated to labour and delivery.

17.5.1 Notification of deaths

All deaths, including deaths deemed unrelated to the IMP will be reported to the Study Coordinator as a serious adverse event (please see Section 16).

17.5.2 Reporting SUSARs

The Study Coordinator, RCSI will notify the main REC and competent authority of all SUSARs. SUSARs that are fatal or life-threatening must be notified to the CA and REC within 7 calendar days after the Study Coordinator has learned of them. Other SUSARs must be reported to the REC and CA within 15 calendar days after the Study Coordinator has learned of them.

17.5.3 Development Safety Update Reports

The Study Coordinator, RCSI will provide the main REC and the competent authority with Development Safety Update Reports (DSUR) which will be written in conjunction with the trial team and the RCSI Sponsorship office. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

17.5.4 Overdose

The study devices will be used as per protocol, administered by a study investigator. Therefore there are no opportunities for an overdose to happen.

17.5.5 Reporting Urgent Safety Measures

If any urgent safety measures are taken the PI/Study Coordinator shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the competent authority and the relevant REC of the measures taken and the circumstances giving rise to those measures.

17.5.6 Notification of Serious Breaches to GCP and/or the protocol

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 subjects of the trial; or (b) the scientific value of the trial.

The Study Coordinator of the clinical trial shall notify the competent authority in writing of any serious breach of –

(a) the conditions and principles of GCP in connection with that trial; or (b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

The Study Coordinator will be notified immediately of any case where the above definition applies during the trial conduct phase. The Study Coordinator's SOP on the 'Notification of violations, urgent safety measures and serious breaches' will be followed.

18 Data management and quality assurance

18.1 Confidentiality

All data will be handled in accordance with the applicable Data Protection legislation

The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data. The subject date of birth and trial identification number, will be used for identification.

18.2 Data collection tools and source document identification

Data will be entered prospectively at the time of the visits into the patient's electronic chart (source data) as is standard protocol within the hospital. All data will be collected by a member of the team from the electronic chart or filled questionnaires and entered into the CRF.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

For data where no prior record exists and which are recorded directly in the eCRF, the eCRF will be considered the source document, unless otherwise indicated by the investigator.

In addition to the above, date(s) of conducting informed consent, trial number, study arm and the fact that the patient is participating in a clinical trial should be added to the patients' medical record contemporaneously.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

18.3 Data handling and analysis

Data handling will be in accordance with Data Protection Legislation. The study coordinator will be the Data Controller and will ensure data security, privacy (anonymization) and archival, in accordance with the Rotunda Hospital IT department data handling policies. The study data will be stored in a centralized and secured area and will not be distributed to a third party. The study data will only be accessed by study personnel, as required, for data monitoring and data analysis.

The software STATA 16 ICE will be used for data entry using pre-specified fields. In addition, the SAS Version 9.4 software will be used for querying data (anomaly detection and rectification), for DSMB reporting and for statistical analysis at study completion. A detailed Statistical Analysis Plan (SAP) will be finalised prior to last-patient last-visit.

19 Record keeping and archiving

Archiving will be authorised by the Study Coordinator following submission of the end of study report. The principle investigator is responsible for archiving the investigator site file. All essential documents will be archived for a minimum of 5 years after completion of trial. Destruction of essential documents will require authorisation from the Study Coordinator.

20 Statistical Considerations

20.1 Outcomes

20.1.1 Primary outcomes

All statistical analysis will be presented in the form of 95% Confidence Intervals, whereby noninferiority (superiority or equivalence) may be inferred. Non-inferiority hypothesis tests will be used to address the primary outcomes in the study. Conditional on non-inferiority being demonstrated, superiority tests may be performed, but it should be noted these are secondary tests and may possibly be under-powered.

Two populations will be used for statistical analysis, intention-to-treat (ITT) and per-protocol (PP), as is usual for non-inferiority testing. The ITT population will consist of all patients randomized and having the primary outcome recorded. The PP population will consist of those patients who adhered to the study protocol procedures.

20.1.2 Secondary outcomes

Secondary outcomes will be compared using confidence intervals and hypothesis tests. However, these will be considered exploratory in nature. No adjustment for multiple testing will be performed.

20.2 Sample size and recruitment

20.2.1 Sample size calculation

A 10% margin was used to determine non-inferiority for all treatment comparisons. An overall 5% level of significance was assumed, with alpha split equally at the 2.5% level for each of the two primary 1-sided non-inferiority comparisons.

In the sample size calculation, SVD rates were assumed to be 70%, 75% and 80% in the Propess, Dilapan-S® (24 hours) and Dilapan-S® (12 hours) groups, respectively.

Non-adherence in the in-patient setting has previously been shown to be approximately 5%. Given a potential non-adherence of 10% in the out-patient setting, this was used to determine the maximum potential sample size (See Table 1). Non-adherence will be monitored monthly to minimize the number of patients to be recruited.

Table 1. Sample size and Power : Total N (N per Group)

Total Sample Size	Statistical Power		
	80%	**85%**	**90%**
N	372 (124)	**423 (141)**	495 (165)
N+5%	393 (131)	444 (148)	519 (173)
N+10%	411 (137)	**465 (155)**	546 (182)

Assuming 85% statistical power and full adherence to the protocol, the minimum total sample size of **423** is required (**141** per treatment group).

Assuming 10% non-adherence, the maximum total sample size of **465** is required (**155** per treatment group).

Based on this sample size, the margin of error is approximately 7% for the SVD rate in any study group.

Given that there is no in-patient group in our study, comparison with an in-patient SVD rate is considered secondary. This is an independent comparison to the primary comparisons and consequently a separate power calculation may be performed without a multiple testing penalty. Assuming a 60% SVD rate for the in-patient population, a 10% non-inferiority margin (equivalently, superiority to 50%), a one-side 2.5% significance level and an N of 141 per study arm, non-inferiority comparisons of either Dilapan-S® or Propess groups to an in-patient rate have very strong statistical power (99%).

20.2.2 Planned recruitment rate

There are approximately 2850 eligible patients per year attending the Rotunda as published annually in the hospital reports. Similar trials in the past have shown an uptake rate of 30% for inpatient induction of labour. With a more conservative uptake rate of about 20% (2850 x 20%=570), we would therefore expect to recruit the required number of participants within 12 months (recruitment will have a maximum allowable duration of 18 months), allowing for dropout rates and those that fit exclusion criteria.

20.3 Statistical analysis plan

20.3.1 Summary of baseline data and flow of patients

All baseline and follow-up data will be presented using summary statistics and graphs (consort diagram, histograms, scatterplots, box-plot) according to study treatment group and study analysis population. A detailed Statistical Analysis Plan will be finalized prior to last-patient-last-visit.

20.3.2 Primary outcome analysis

The non-inferiority analyses for the co-primary outcome will involve significance testing (at the 2.5% level of significance) and confidence intervals (97.5%) for simple differences in proportions. The analyses will be performed using an intention-to-treat analysis and a per-protocol analysis. SAS Version 9.4 will be used to analyse the data.

20.3.3 Secondary outcome analysis

Exploratory data analysis will be performed on the secondary outcomes.

20.3.4 Sensitivity and other planned analyses

Multiple (multivariate) logistic regression for the primary endpoints to adjust for potential prognostic variables will be performed. Such analysis will be deemed exploratory in nature and not considered the primary analysis.

20.4 Randomisation methods

Patients will be randomized using simple random allocation to either Dilapan-S® (12-hour insertion or 24-hour insertion) or Propess in a 1:1:1 ratio using a block size of 6 via a computer-generated randomization procedure (software SAS Version 6.4).

20.5 Interim analysis

No interim analysis will be performed.

20.6 Other statistical considerations

Missing data mechanisms will be explored with respect MNAR (missing not at random) and potential mechanisms associated will assessment biases will be explored statistically.

21 Name of Committees involved in trial

The Chief Investigator (CI) will be responsible for selecting the members of the Trial Management Group (TMG), Trial Steering Committee (TSC) and Data Safety Monitoring Board (DSMB). The CI will organise the structure, frequency and agenda of meetings. A member of the Study Coordinator office (RCSI) will sit on the TMG to provide advice and maintain trial oversight. The terms of reference for the TMG, TSC and DSMB will be developed by the Investigator and the Study Coordinator and will be reviewed by the Study Coordinator prior to final approval to ensure they meet the requirements.

Trial Management Group (TMG):

The Trial Management Group will meet two-monthly and be responsible for the day-to-day management of the trial and include the PI, a Study Coordinator representative collaborators, statistician, trial manager and research assistants. The TMG will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

The TMG will report to the TSC and will ensure that the study is conducted in compliance with the protocol, GCP and applicable regulations. The responsibilities will include (but are not limited to):

- Reporting to the Trial Steering Committee
- Identification of trial sites
- Confirmation that all approvals are in place before release of the IMP and the start of the trial at each site
- Provision of training about the trial at each site
- Provision of trial materials to each site
- Establishment of a data management centre
- 24-hour advisory support
- Provision of regular information about the progress of the study to collaborators
- Response to any questions (e.g. from collaborators) about the trial
- Data security and quality and observation of data protection laws
- Safety reporting
- Assurance that trial is conducted in accordance with the ICH GCP
- Statistical analysis
- Publication of trial results

Data Safety Monitoring Board (DSMB):

The outcome objective of the DSMB is to provide impartial and objective assessment of clinical trial safety data. Independence of the DSMB promotes:

- Greater objectivity relative to overall clinical benefit risk assessment
- Increased credibility of the clinical trial data
- Enables modification to trial, where necessary, in response to new external DSMB recommendation without introducing bias.

The independent DSMB members will review clinical trial data to evaluate safety and scientific validity of the clinical trial. Review of the full safety data from the clinical trial will enable impartial conclusion and recommendation which may be to do one of the following:

- Continue with the clinical trial as planned
- Continue with the clinical trial but amend the protocol prior to moving to next phase of clinical trial
- Stop the clinical trial

Trial Steering Committee (TSC):

The TSC is an independent body whose members do not have a role in running the clinical trial. For the purpose of this Trial, the TSC will be comprised of the TMG members with the addition of one independent person and will meet at a frequency outlined in the terms of reference. The role of the TSC is to oversee and supervise the progress of the clinical trial and ensure the clinical trial is being conducted in accordance with GCP and applicable regulations. The TSC will agree to any protocol amendments and provide advice to the CI on all aspects of the clinical trial. The TSC will make major decisions regarding the continuation of the clinical trial or substantial amendments to the protocol based on the recommendations of the DSMB and ethics committee. The responsibilities of the TSC will be documented in the Terms of Reference.

The terms of reference for these committees will need to be provided in separate documents

22 Direct Access to Source Data/Documents

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.

23 Ethics and regulatory requirements

The Study Coordinator will ensure that the trial protocol, patient information leaflet, informed consent form, GP letter and submitted supporting documents have been approved by the appropriate competent authority and a research ethics committee, prior to any patient recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation.

Before the site can enrol patients into the trial, the Principal Investigator or designee must apply to the hospital for permission to conduct the study and be granted written permission. It is the responsibility of the Chief Investigator/ Principal Investigator or designee at each site to ensure that all subsequent amendments gain the necessary approval. 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 17.5.5 for reporting urgent safety measures).

Within 90 days after the end of the trial, the CI/Study Coordinator will ensure that the main REC and the competent authority is 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.

24 Monitoring requirement for the trial

The Study Coordinator, RCSI will assign an independent monitor who will visit the investigator intermittently to validate compliance of the protocol to GCP, the maintenance of the study related records, and the extensiveness and accuracy of a proportion of CRF entries compared to source data. The investigator will co-operate with the monitor to ensure that any potential discrepancies are resolved.

Monitoring procedures include a site initiation visit designed to clarify all prerequisites before the trial commences at the site, interim site monitoring visits and study close-out visits. The study will be monitored by regular scheduled visits to site and on-going communication via telephone and e-mail. During site visits the monitor will review; original patient records for the patient group; CRFs; drug accountability records; investigator site file and document retention. Study procedures will be observed by the monitor and any issues will be discussed with the PI or designee as necessary. At a minimum, source documentation will be available to substantiate subject identification, eligibility, and participation; proper informed consent procedures; dates of visits; adherence to protocol procedures; records of safety and efficacy parameters; adequate reporting and follow-up of AEs; administration of concomitant medication; drug receipt/dispensing/return records; study drug administration information; and dates of subject completion, discontinuation from treatment, or withdrawal from the study, including the reason if appropriate.

CRF entries will be verified with the source documentation, if applicable (in some cases there are no source pages, therefore verification is not necessary). If any data, signatures, or forms are missing or incorrect, the Investigator or designee will be informed and corrections will be made. Direct access to all source documents must be guaranteed by the PI, who must provide support at all times for these activities.

25 Finance

Funding for this study has been obtained through The Rotunda Foundation (Charity Registration CHY20091) and Medicem Technology s.r.o.

26 Insurance

The Rotunda Hospital will indemnify claims from participants for injury caused by their participation in the clinical trial. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participants of the clinical trial.

27 Publication policy

All proposed publications will be discussed with the Study Coordinator, RCSI prior to publishing other than those presented at scientific forums/meetings. Please refer to the RCSI publication policy.

28 Statement of compliance

The trial will be conducted in compliance with the approved protocol, the ROI Regulations, ICH GCP and the applicable regulatory requirement(s).

29 Appendices

Appendix 1: Instructions for use for Dilapan-S®

Appendix 2: SmPC for Propess

Appendix 3: RCSI Expedited Safety Reporting SOP

Appendix 4: IMP Labels

Appendix 5: Maternal Induction of Labour Questionnaire

30 References

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Study Protocol: Home Induction Trial

1. Study Title

Full title of trial	The Home Induction trial: A randomised open-label trial to assess outpatient induction of labour, and compare efficacy of Propess vs Dilapan-S® for induction of labour at 39 weeks' gestation in normal risk nulliparous women.
Short title	IND HOME trial
Version and date of protocol	Version 5, 28-Nov-2022
Sponsor:	Rotunda Hospital
Funder (s) :	Rotunda Hospital
EudraCT no	**2019-004697-25**
ACTIVE IMP(s):	Propess Dilapan-S®
PLACEBO IMP(s):	None
Phase of trial	Phase 3
Sites(s)	Rotunda Hospital

Table of Contents

4. List of abbreviations

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CS	Caesarean Section
CTA	Clinical Trial Authorisation
CTG	Cardiotocograph
CTIMP	Clinical Trial of Investigational Medicinal Product
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
EMEA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IOL	Induction of labour
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
MA	Marketing Authorisation
PI	Principal Investigator
PIL	Participant Information Leaflet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person for release of trial drug
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

7. Summary

Title:

The Home Induction trial: A randomised open-label trial to assess efficacy of inpatient vs outpatient induction of labour, and compare efficacy of Propess vs Dilapan-S® for induction of labour at 39 weeks' gestation in normal risk nulliparous women.

Short title: The Home Induction trial: Efficacy of outpatient induction of labour at 39 weeks with Dilapan-S® vs Propess

Trial medication: **Propess** Dinoprostone 10mg vaginal delivery system. The insert contains 10mg dinoprostone which is released over 24 hours.
Dilapan-S® is an osmotic hygroscopic dilator produced from a patented Aquacryl hydrogel.

Phase of trial: Phase IV

Objectives:

Primary objective:

To demonstrate non-inferiority in the efficacy of Dilapan-S® (12 hours or 24 hours insertion) to Propess for outpatient induction of labour at 39 weeks' gestation in otherwise uncomplicated, normal risk* nulliparous women.

* A pregnancy is considered "normal-risk" when there are no active complications and there are no maternal or fetal factors that place the pregnancy at increased risk for complications. Specifically, the following conditions should be met to consider a pregnancy to be normal risk:

- Singleton pregnancy
- Cephalic presentation
- Term gestation (37-39 weeks gestational age)
- Maternal pre-pregnancy body mass index < 35kg/m2
- Maternal age of ≥ 18 and < 40 years
- No evidence of the following conditions:
- Pre-pregnancy diabetes
- Gestational diabetes
- Pre-pregnancy hypertension
- Cervical cerclage in situ
- Premature rupture of membranes
- Congenital fetal anomalies

Population: Normal risk nulliparous women with no medical complications who have no contraindications to induction of labour.

Secondary objectives:

1) To compare the Dilapan-S® (12 hours) group to the Propess group in the primary endpoint and secondary endpoints *(see Section 10.3 for further details)*
2) To compare the the Dilapan-S® (24 hours) group to the Propess group in the primary endpoint and secondary endpoints *(see Section 10.3 for further details)*
3) To compare the Dilapan-S® (12 hours) group to the Dilapan-S® (24 hours) group in the primary endpoint and secondary endpoints *(see Section 10.3 for further details)*
4) To compare rates of vaginal delivery in the Dilapan-S® 12-hour group, the Dilapan-S® 24-hour group and the Propess at 36 hours, 48 hours and 48 hours respectively from insertion time to delivery *(see Section 10.3 for further details)*

Type of trial:	A Phase 3 trial in normal risk nulliparous women at 39 weeks' gestation.
Trial design and methods:	A randomised open-label trial to assess and compare efficacy of Propess vs Dilapan-S® for induction of labour at 39 weeks' gestation in normal risk nulliparous women. Additionally, non-inferiority will be compared in the Dilapan-S® 24 hour arm versus Dilapan-S® 12 hour arm.
Trial duration per participant:	8 weeks
Estimated total trial duration:	30 months
Planned trial sites:	Single-site
Total number of participants planned:	327
Main inclusion/exclusion criteria:	**Inclusion criteria** • Normal risk nulliparous women (as defined in trial objectives) • Age ≥18 and <40 years • Singleton pregnancy • No contraindications to induction of labour

- Must agree to outpatient induction at 39 weeks
- No relevant medical issues in or outside of pregnancy

This is assessed by a doctor on a case by case basis. Relevant medical issues would be inclusive of the systems disorders as in exclusion criteria. Non relevant medical issues may include, but are not limited to: anxiety/depression not requiring medications, history of urinary tract infections, past history of sexually transmitted infections that have been successfully treated, history of abnormal cervical smear tests, incidence of human papillomavirus, varicose veins, minor surgery or any surgery that would not result in contraindication to induction of labour)

- Must live within 30 minutes or 15km of the hospital and have transport to hospital at all times during induction period
- A normal amniotic fluid index (AFI) at 39 weeks' gestation is between 8 cm and 20 cm
- Biophysical Profile Score (BPS) is 8/8
- Bishops score <6 at Visit 2

Exclusion criteria

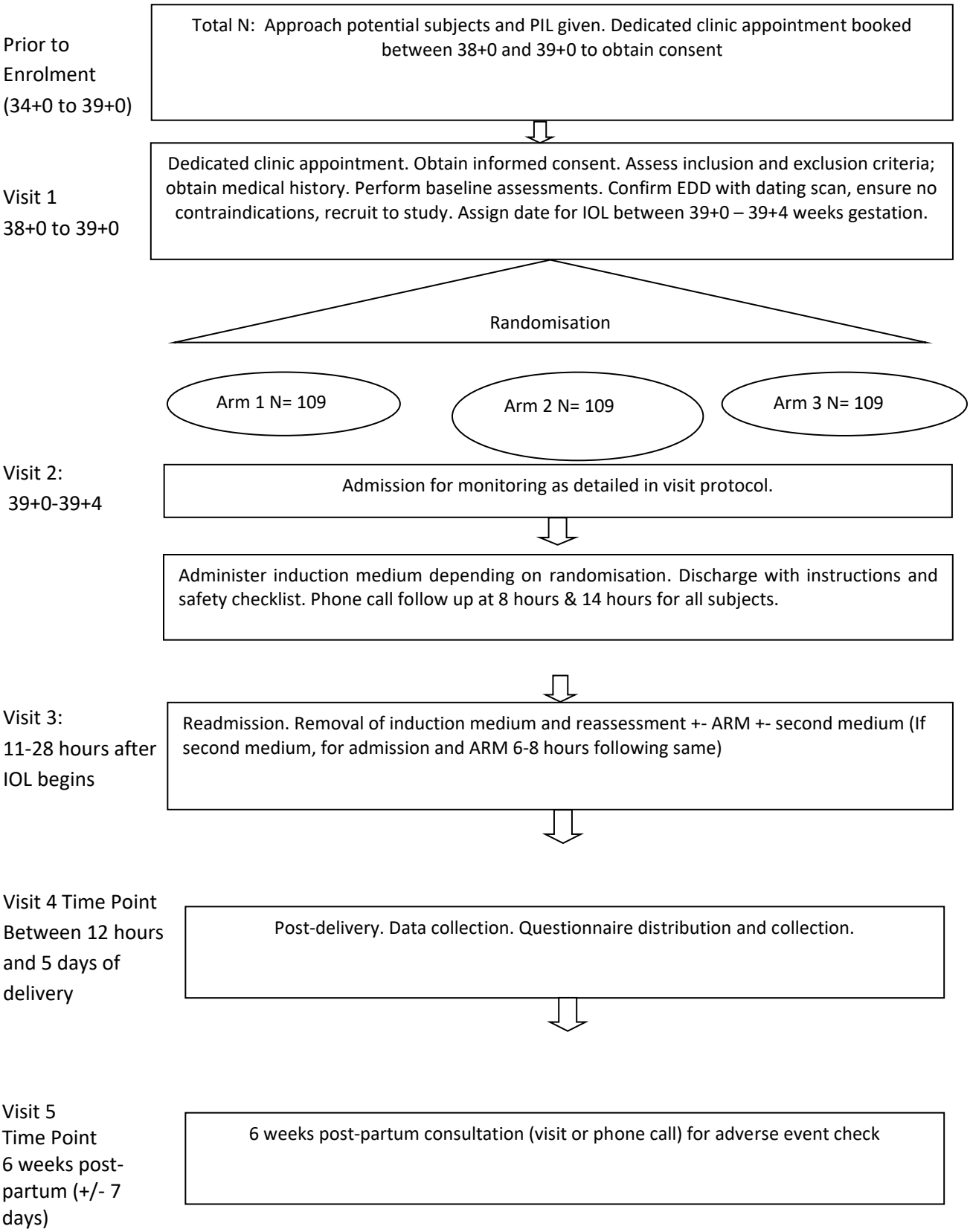
- Multiparous women
- Women with uterine scar
- Women with low lying placenta
- Women with BMI > 35 kg/m^2
- Multiple gestation
- Known fetal anomaly or fetal growth restriction or oligohydramnios
- Known maternal health problem e.g. hypertensive disease, cardiac disease, renal disease, diabetes, pulmonary disease, hepatic disease which would directly affect the risk status of the woman. This is assessed clinically on a case by case basis.
- Women with no transport to hospital or women who live >30 minutes or >15km from the hospital
- Patients who have difficulty understanding the required protocol and follow up instructions (e.g. language barriers)
- Women <39+0 or greater than 39+4 weeks' gestation at time of induction of labour (Visit 2).

    - Gestational age will be based on initial dating scan between 7-14 weeks, which confirms gestational age by CRL.
- Any factor which is a contraindication to induction of labour
- Contraindications to trial treatment include patients that fall into any of the following categories:

    - If labour has started.
    - If oxytocic drugs and/or other labour induction agents have been given.
    - When strong prolonged uterine contractions would be inappropriate.
    - Patients who have had previous major uterine surgery, e.g. Caesarean section, myomectomy
    - Patients with a clinical suspicion for cephalopelvic disproportion
    - Patients with fetal malpresentation
    - Patients with suspicion or evidence of non-reassuring fetal testing
    - Who have had previous major surgery (e.g. other than biopsies and cervical abrasion) or rupture of the uterine cervix
    - When there is current pelvic inflammatory disease, unless adequate prior treatment has been instituted.
    - Patients with hypersensitivity to dinoprostone or to any of the excipients listed in the SmPC for Propess/Prostin
    - Patients with placenta previa or unexplained vaginal bleeding during the current pregnancy.
    - Patients with evidence or any sign of infection, including genital tract infection

Statistical methodology and analysis:	Comparisons of proportions of patients with successful vaginal delivery will be compared using confidence intervals for differences in proportions. All other comparisons will be considered secondary and no adjustment for multiple comparisons will be made. The primary analysis population for non-inferiority will be the per-protocol population, supported by an intention-to-treat analysis.

Schematic of Study Design:



9. Introduction

9.1 Background

Induction of labour (IOL) has become quite topical in recent years, with studies examining the role of IOL in accomplishing lower caesarean section rates, reduced neonatal morbidity and mortality rates, and improved maternal experience. These outcomes have been examined through RCTs, observational and qualitative studies amongst others.

There is a growing body of evidence to suggest that IOL at 39 weeks' gestation in otherwise uncomplicated (normal risk) nulliparous women decreases the primary caesarean section rate, is cost-effective, does not result in increased perinatal adverse outcomes, and may decrease adverse outcomes.

What is not clear from the literature is the ideal method of achieving successful induction of labour in such patients, and if this could be a process that can be managed outside of the hospital setting in the normal risk nulliparous group, thus reducing resource utilisation and allowing overall better experiences within the cohort being induced.

The IND HOME trial aims to assess two popular methods of induction, both of which allow the patient to return home for 12 or 24 hours after initiation of IOL. The main issue with offering IOL to women at 39 weeks is that there is a paucity of space and beds that would be needed in the cervical ripening stage of IOL, meaning that we cannot feasibly offer this choice to women at present. The outcome is assessment of vaginal delivery by any means at any time (overall vaginal delivery rate), assessing suitability of both methods as effective cervical ripening agents.

Bearing in mind the increasing caesarean delivery rates worldwide, the potential for any decrease in the primary caesarean section rate could result in significant decreases in maternal morbidity and mortality, were a safe and attainable protocol for cervical ripening and induction of labour to be found. The promise of an overall safer option for mother and baby, and ability to offer this to our target cohort of normal risk nulliparous women would be a huge advance in obstetric care. Finding a way in which to do this effectively at home is critical for our ability to offer IOL to women safely. It would also likely lead to an increase in satisfaction in terms of mothers, who can enjoy home comforts whilst this stage of cervical ripening is initiated.

9.2 Preclinical data

Preclinical studies have demonstrated that dinoprostone is a locally acting substance which is rapidly inactivated and thus it has no significant systemic toxicity. The hydrogel and polyester polymers are inert compounds with good local tolerability. Reproduction toxicity, genotoxic or carcinogenic effects of the polymers have not been investigated but systemic exposure is negligible[i].

9.3 Clinical data

It is evident in recent research that induction at 39 weeks may result in lower adverse outcomes for both mother and baby. Chen et al[ii] found that in the multiparous woman, the risk of composite adverse neonatal outcome and composite adverse maternal outcome was lower at 39 weeks' than at 40 & 41 weeks' gestation. The ARRIVE trial[iii] showed that the caesarean delivery rate was lower in normal risk nulliparous women who underwent IOL at 39 weeks' gestation compared to expectant management, as well as lower rates of hypertension, but with no change in costs for the centre, and no change in adverse neonatal outcome.

In terms of outpatient IOL, a Cochrane review[iv] examined 4 published and unpublished randomized and quasi randomized trials with a combined total of 1,439 women. These trials assessed different methods of induction in the outpatient setting; thus, the results were not amalgamated. In those trials examined, vaginal PGE2 was used in two; and the outcomes showed no evidence of a difference in the women requiring instrumental delivery, with a similar rate of hospital stay in both groups. One study employed the use of a prostaglandin pessary in 300 women. There was no difference between groups for most review outcomes, including successful induction of labour. Mechanical induction with a Foley catheter was used in one study comprising 111 women. In this study there was no difference between groups.

A more recent Cochrane review in 2017[v] assessed outpatient vs inpatient induction for improving patient outcomes. This review included 34 RCTs comprising 11 different methods for labour induction with 5003 randomised women, where women received treatment at home or were sent home after initial treatment and monitoring in hospital. They concluded that outpatient IOL appears feasible and safe, but that in general there is insufficient evidence to detect differences. The review specifically suggested that there have been very few direct comparisons between different methods of labour induction in outpatient settings.

A Portuguese RCT[vi] examined the use of mechanical cervical priming with a Foley catheter in the outpatient vs inpatient setting, finding that outpatient priming was as safe and effective as inpatient priming, but with a shorter hospital stay, and less caesarean deliveries for failed induction. Recent studies have compared safety indices of balloon catheters with Dilapan-S® [vii] and found that Dilapan-S® is not inferior to the Foley balloon for cervical ripening at term. Overall advantages of Dilapan-S® included FDA approval, the absence of anything protruding from the vagina, favourable safety profile, and the lack of applying tension to a Foley catheter needed for use, as well as patient satisfaction.

A survey of outpatient IOL in the UK[viii] showed that 16.5% of hospitals within the UK already provide outpatient IOL for post-dates singleton normal risk pregnancies. Of those providing the service 84% were using Propess as the method of initiating labour, while others used dinoprostone gel or isosorbide mononitrate. A further 1.2% were aiming to start an outpatient IOL service within the near future. Notably, at the time of the survey, no hospital was using mechanical dilators such as Dilapan-S® or an intracervical balloon.

A prospective pilot study was carried out by Crosby et al [ix]in the National Maternity Hospital, Dublin who examined Propess and Dilapan-S® for use for inpatient IOL in the post-dates setting. This was a single-centre, prospective, observational pilot study (non-blinded / non-randomized) in which 52

women received either Dilapan-S® or Propess for IOL. The study found that Dilapan-S® was an acceptable, safe form of induction of labour in post-dates uncomplicated nulliparous pregnancy.

Following the ARRIVE trial, whereby women were induced at 39 weeks' gestation, the data would suggest that there was a decrease in frequency of caesarean delivery. It also noted that the incidence of hypertension was reduced. Overall the trial showed no difference in cost of healthcare in this cohort. It did not find any difference in primary perinatal outcome; however, the trial was notably not powered to assess this outcome and it was not a primary endpoint. In terms of outpatient vs inpatient protocols, the best available evidence appears to show no difference in safety data between inpatient and outpatient induction.

Some studies have examined the overall experience of outpatient induction from the maternal perspective through qualitative methods [x] and have found that in general, women liked the opportunity to remain at home, and felt the home setting offered freedom, security and reassurance compared to the hospital, which was viewed as constraining.

Overall, evidence points towards outpatient induction of labour as being safe, effective and well received by women. Furthermore, evidence for inpatient and outpatient induction of labour by mechanical methods such as Dilapan-S® shows it to be safe and effective as a cervical ripening agent. Propess is a well-established method of induction in both inpatient and outpatient settings and is widely used within Ireland and the UK.

9.4 Rationale and risks/benefits

The rationale of this study is to investigate methods (Propess vs Dilapan-S®) of outpatient-based induction of labour at 39 weeks in normal risk nulliparous women.
Currently the Rotunda and the National Maternity Hospital are the only known hospitals in Ireland performing outpatient IOL. This is offered to normal risk nulliparous and multiparous women when their induction process begins with Propess or Dilapan-S for uncomplicated post-dates (i.e. 41+3/41+5 as per hospital protocol) induction.

This study will recruit women as per the inclusion and exclusion criteria as above, and a date for IOL will be set for between 39+0 and 39+4 weeks gestation. The assessments will take place in an assigned ward, where the patient will have fetal monitoring and maternal monitoring (CTG and recording of vitals, respectively) and a study investigator will assess the patient and begin one of two methods based on the randomization to one of two groups.

This study will aim to assess if Propess and Dilapan-S® have any major differences in failing to achieve a vaginal delivery within a given time frame, as described above. It will also assess if there is any difference in efficacy in terms of timing of Dilapan-S® (i.e. Dilapan-S® for 12 hours vs 24 hours). If Dilapan-S® is shown to be non-inferior, it would allow us to adapt practice in order to introduce this method for outpatient IOL, improve the process and allow for safe and effective methods of outpatient IOL. It may also be the basis of new guidelines for induction of labour nationally. In previous years, prostaglandin gel would have been the main form of hormonal cervical ripening, and Foley catheters or laminaria used as mechanical. However, Propess has been extremely popular due to its reduction

in necessary vaginal examinations (prostaglandin gel required reassessment every 6 hours vs Propess every 24 hours); and the ability to remove Propess if any side effects occur. Propess is now commonly used as the induction method of choice in many women for these reasons. A Foley catheter has been used in order to provide a mechanical induction method for those in whom hormonal methods are contraindicated. However, this necessitated taping the catheter to the patient's leg in order to keep pressure, which is not to the liking of many patients. Laminaria were originally made from the dried stems of laminaria seaweed, which was a biological material and so had the side effect of potential reactions to this.

Both methods of IOL will be used as intended within their license. There will be no changes to suggested timing or delivery of either device- i.e. Propess (1 delivery system) will be inserted and the patient allowed to return home before removal by 24 hours. Dilapan-S® (the required number of rods as per manufacturer guidelines) will be inserted and the patient allowed to return home before removal by either 12 hours or 24 hours.

9.5 Assessment and management of risk

Induction of labour is a widely studied area. Initially and currently most centres will offer IOL to post-dates (i.e. 40+ weeks gestation) in accordance with their local guidelines in order to decrease risks of stillbirth, the incidence of which increases sharply after 42 weeks' gestation. However, IOL has routinely been offered earlier due to maternal age, suspected macrosomia, hypertensive disorders of pregnancy, and medical issues in the mother or baby. In general, IOL between 41-42 weeks has been shown to reduce the risk of caesarean section compared to expectant management, and recently the ARRIVE trial has shown that IOL at 39 weeks resulted in a further decrease in CS rate by 4% if IOL took place at 39 weeks[iii].

Therefore, we know that generally, IOL is a safe endeavour, and appears to be safer still at 39 weeks. A further study published in August 2019 showed similar findings in multiparous women, showing decreased perinatal morbidity without an increase in caesarean delivery rate in the IOL at 39 weeks group in comparison to expectant management[xi]. The maternal complications of prolonged pregnancy are linked closely with the risks of labour dystocia, genital tract trauma, CS, PPH and anxiety[xii].

As described above, outpatient IOL has been described as safe in multiple studies and a Cochrane review, but lacks evidence on efficacy. Therefore this study aims to provide further high quality evidence on rates of vaginal delivery after outpatient IOL at 39 weeks' gestation compared to published inpatient rates at 39 weeks gestation.

9.6 Potential Risks

Propess:
Risks of hyperstimulation with Propess have been reported as between 0-5% in various studies. Hyperstimulation can be treated with tocolytics such as terbutaline if there are signs of non-reassuring fetal testing, as per standard practice. An advantage of using Propess over prostaglandin gel preparations is that once removed, dinoprostone in this form has a half-life of 1-3 minutes[i], meaning that hyperstimulation that is reported with Propess is often resolved by removal of the pessary alone.

With respect to outpatient IOL, patients are instructed to return to the hospital if they are experiencing persistent abdominal pain or increased frequency of contractions suggestive of hyperstimulation.

Risks of Propess as per SmPC:
The most commonly reported adverse drug reactions in placebo-controlled and active comparator efficacy clinical trials (N=1116) were “fetal heart rate disorder” (6.9%), “uterine contractions abnormal” (6.2%) and “abnormal labour affecting foetus” (2.6 %).

The table below displays the main ADRs distributed by system organ classes (SOC) and frequency. Further, the ADRs seen during post-marketing experience are mentioned with unknown frequency.

System organ class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Not known: (cannot be estimated from the available data)**
Blood and lymphatic system disorders			Disseminated intravascular coagulation
Immune system disorders			Anaphylactic reaction Hypersensitivity
Nervous system disorders		Headache	
Cardiac disorders	Fetal heart rate disorder [1]*		
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders		Neonatal respiratory distress related conditions	
Gastrointestinal disorders			Abdominal pain, Nausea, vomiting, diarrhoea
Hepatobiliary disorders		Neonatal hyperbilirubinaemia	
Skin and subcutaneous tissue disorders		Pruritus	
Pregnancy, puerperium and perinatal conditions	Abnormal labour affecting fetus [2]* Uterine contractions abnormal Meconium in amniotic fluid Uterine tachysystole, uterine hyperstimulation, uterine hypertonus	Postpartum haemorrhage, Premature separation of placenta, Apgar score low Arrested labour Chorioamnionitis Uterine atony	Anaphylactoid syndrome of pregnancy Fetal distress syndrome [3]* Fetal death, still birth, neonatal death[4]*
Reproductive system and breast disorders		Vulvovaginal burning sensation	Genital oedema
General disorders and administration site conditions		Febrile disorders	

Injury, poisoning and procedural complications			Uterine rupture

Adverse reactions observed in clinical studies are presented according to their incidence, post authorisation reported adverse reactions are presented in the column frequency unknown.

1* “Fetal heart rate disorder” was in clinical studies reported as “fetal heart rate abnormalities”, “fetal bradycardia”, “fetal tachycardia”, “unexplained absence of normal variability”, “fetal heart rate decreased”, “fetal heart rate deceleration”, “early or late decelerations”, “variable decelerations”, “prolonged decelerations”.

2* “Abnormal labour affecting foetus” as expression for hyperstimulation syndrome was in clinical studies reported as “uterine tachysystole” combined with “late decelerations”, “fetal bradycardia”, or “prolonged decelerations ”

3* “Fetal distress syndrome” was also reported as “fetal acidosis” , “pathological CTG”, “fetal heart rate abnormalities”, “intrauterine hypoxia” or “threatening asphyxia”. The term itself is unspecific, has a low positive predictive value and is often associated with an infant who is in good condition at birth.

4* “Fetal death, stillbirth, and neonatal death have been reported after application of dinoprostone, especially following the occurrence of serious adverse events such as uterine rupture”

Dilapan-S®:

Risks of hyperstimulation with Dilapan-S® have been reported as ‘very low’. At the time of writing, there was one case of hyperstimulation with Dilapan-S® reported in the e-registry, with no established causality.

The methods used in this study are used as per manufacturer and licencing guidelines, and therefore equate to the overall risk of use, with no theoretical higher risk than in the general population.

Potential risks of Dilapan-S® include: (as quoted by manufacturer information)

- Device entrapment and/or fragmentation or detachment of the handle
- Device expulsion
- Device retraction into the uterus
- Discomfort or bleeding during and/or after insertion
- Spontaneous rupture of membranes
- Spontaneous onset of labour
- Injury to the birth canal (cervical laceration)

Advice from information leaflet for Dilapan-S®

- The patient should be advised to report any excessive bleeding, pain, or increase in temperature.
  The patient should avoid bathing, douching and refrain from sexual intercourse while Dilapan-S® is in place.

Side effects:

- The patient may experience a so called “vaso-vagal reaction” also known as “faintness”. This temporary status of weakness, paleness, nausea, dizziness or loss of consciousness may be caused by cervical manipulation. By remaining recumbent for 3 to 10 minutes these symptoms usually disappear.

The methods used in this study are used as per manufacturer and licencing guidelines, and therefore equate to the overall risk of use, with no theoretical higher risk than in the general population.

9.7 Potential Benefits

The benefits are that induction at this stage may decrease the risk of having a caesarean section. It may also decrease the risk of complications for mothers and babies.

Being induced at 39 weeks may also allow for delivery before complications occur later in the pregnancy. For example, meconium stained liquor is more common after 40 weeks of gestation. There is a decreased risk of shoulder dystocia, a decreased risk of OASI, and a decreased risk of PPH. There is a decreased risk of NICU admission for various reasons as detailed in the literature review above.

This study may help formulate an effective plan for induction of labour in many women in the comfort of their own homes in the future, benefiting a multitude of future patients.

Additionally, there are potential benefits to maternity services including a reduction in length of antenatal stay in hospital, less strain on maternity units / resources, a potential reduction in financial costs and avoidance of unnecessary hospital admissions.

10 Objectives and Outcome Measures

10.1 Primary objective

To demonstrate non-inferiority in the efficacy of Dilapan-S® (12 hours or 24 hours insertion) to Propess for outpatient induction of labour at 39 weeks' gestation in otherwise uncomplicated, normal risk* nulliparous women.

* A pregnancy is considered "normal-risk" when there are no active complications and there are no maternal or fetal factors that place the pregnancy at increased risk for complications. Specifically, the following conditions should be met to consider a pregnancy to be normal risk:

- Singleton pregnancy
- Cephalic presentation
- Term gestation (37-39 weeks gestational age)
- Maternal pre-pregnancy body mass index < 35kg/m2
- Maternal age of ≥ 18 and < 40 years
- No evidence of the following conditions:
- Pre-pregnancy diabetes
- Gestational diabetes
- Pre-pregnancy hypertension
- Cervical cerclage in situ
- Premature rupture of membranes

- Congenital fetal anomalies

10.2 Secondary Objective(s)

1)To compare the Dilapan-S® (12 hours) group to the Propess group in the primary endpoint and secondary endpoints (see Section 10.3 for further details)

2)To compare the Dilapan-S® (24 hours) group to the Propess group in the primary endpoint and secondary endpoints (see Section 10.3 for further details)

3)To compare the Dilapan-S® (12 hours) group to the Dilapan-S® (24 hours) group in the primary endpoint and secondary endpoints (see Section 10.3 for further details)

4)To compare rates of vaginal delivery in the Dilapan-S® 12-hour group, the Dilapan-S® 24-hour group and the Propess group at 36 hours, 48 hours and 48 hours respectively from insertion time to delivery (see Section 10.3 for further details)

10.3 Study Outcome Measures

For all study participants, information will be recorded in the electronic chart as is standard for all patients in the hospital. Data on all of the above primary and secondary objectives will be collected and collated.

At the initiation of induction, the gestational age and exact time of initiation of induction will be recorded.

A questionnaire will be given to participants to complete during their postnatal admission in the first feasible instance following delivery in order to assess their satisfaction scores with the process of outpatient induction.

10.3.1 Primary outcome measure

The primary outcome measure (efficacy measure) is failure to achieve vaginal delivery (or, equivalently, operative vaginal delivery or SVD) at any time. This will allow assessment of effective methods of IOL in the outpatient setting. The window for induction will be 39+0 to 39+4 weeks gestation.

10.3.2 Secondary outcome measures

1. Overall change in Bishop score before and after cervical ripening
2. Rates of vaginal delivery at 36 hours after insertion of either Propess or Dilapan-S®
3. Rates of vaginal delivery at 48 hours after insertion of either Propess or Dilapan-S®
4. The need for second induction modality
5. Rates of hyper-stimulation*
6. Rate of failed induction

7. Overall length of stay in hospital
8. Rates of adverse neonatal outcome
9. Rates of adverse maternal outcomes
10. Maternal satisfaction scores with the outpatient induction process
11. Caesarean delivery rates, categorized by “overall rate”, “rate for failure to progress/failed induction”, and “rate for non-reassuring fetal testing”
12. Analgesia use in each group, including rates of epidural
13. Compare rates of 39 weeks’ successful vaginal delivery in the outpatient setting to rates of successful vaginal delivery in the inpatient setting**.

**defined as more than 7 contractions in a 15 minute time period persistently for more than 30 minutes and requiring a medical intervention (such as a clinical decision to remove the Propess/Dilapan or administer a medication such as Terbutaline).*

***defined as a group of low risk nulliparous women who did not undertake elective induction of labour at 39 weeks as part of this trial.*

The primary objectives will therefore assess the efficacy of achieving labour with each of the study induction methods. The secondary objectives will assess other efficacy measures, safety measures and maternal satisfaction scores which are important factors in deciding whether this is a feasible option long term, and risk stratification in this process. Although many studies have shown both induction mediums to be low risk, it is important to compare the outcomes as above in order to guide the best possible IOL methods and create the most appropriate protocol for women to undergo IOL.

11 Trial design

11.1 Overall design

This study is an open-label parallel group single-centre trial.

Participants are normal risk nulliparous women who have no pregnancy-related or medical contraindication to IOL. Women will be randomized to one of three induction groups- Dilapan-S® (12-hour insertion or 24-hour insertion) or Propess, which will be initiated between 39+0 and 39+4 weeks’ and then allowed to return home for either 12 or 24 hours. They will be readmitted 12/24 hours later and reassessed in order to continue with induction of labour.

Patient recruitment will take place over 30 months within a single centre. The study will recruit a maximum 109 women for each study arm. Total duration of participants involvement in the trial will be 8 weeks to allow for postpartum follow up.

The protocol and visit specifics are detailed below in section 13.4, 13.5 and 13.6.

11.2 Selection of Subjects

This trial will be conducted at one hospital site (Rotunda Hospital) Identification of potential subjects will be from the antenatal clinic lists. Potential participants who may wish to enquire about the study through advertising will also be able to contact the investigator. The expected number of participants that will be available for screening over 30 months is approximately 7500, with a sample size of 327 to be recruited.

11.3 Inclusion criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Provide signed and dated informed consent form
- Willing to comply with all study procedures and be available for the duration of the study
- Normal risk nulliparous women (as defined in trial objectives)
- Age ≥18 and <40 years
- Singleton pregnancy
- No contraindications to induction of labour
- Must agree to outpatient induction at 39 weeks
- No relevant medical issues in or outside of pregnancy
    - This is assessed by a doctor on a case by case basis. Relevant medical issues would be inclusive of the systems disorders as in exclusion criteria. Non relevant medical issues may include, but are not limited to: anxiety/depression not requiring medications, history of urinary tract infections, past history of sexually transmitted infections that have been successfully treated, history of abnormal cervical smear tests, incidence of human papillomavirus, varicose veins, minor surgery or any surgery that would not result in contraindication to induction of labour)
- Must live within 30 minutes or 15km of hospital and have transport to hospital at all times during induction period
- A normal amniotic fluid index (AFI) at 39 weeks' gestation is between 8 cm and 20 cm
- Biophysical Profile Score (BPS) is 8/8
- Bishops score <6 at Visit 2

11.4 Exclusion criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Multiparous women
- Women with uterine scar
- Women with low lying placenta
- Women with BMI > 35 kg/m^2
- Multiple gestation
- Known fetal anomaly or fetal growth restriction or oligohydramnios

- Known maternal health problem e.g. Hypertensive disease, cardiac disease, renal disease, diabetes, pulmonary disease, hepatic disease which would directly affect the risk status of the woman. This is assessed clinically on a case by case basis.
- Women with no transport to hospital or women who live >30 minutes or >15km from the hospital
- Patients who have difficulty understanding the required protocol and follow up instructions (e.g. language barriers)
- Women <39+0 or greater than 39+4 weeks' gestation at the time of induction of labour (Visit 2)
    - Gestational age will be based on initial dating scan between 7-14 weeks, which confirms gestational age by CRL.
- Any factor which is a contraindication to induction of labour
- Contraindications to trial treatment include patients that fall into any of the following categories:

    - If labour has started.
    - If oxytocic drugs and/or other labour induction agents have being given.
    - When strong prolonged uterine contractions would be inappropriate.
    - Patients who have had previous major uterine surgery, e.g. Caesarean section, myomectomy
    - Patients with a suspicion for cephalopelvic disproportion
    - Patients with fetal malpresentation
    - Patients with suspicion or evidence of non-reassuring fetal testing
    - Who have had previous major surgery (e.g. Other than biopsies and cervical abrasion) or rupture of the uterine cervix
    - When there is current pelvic inflammatory disease, unless adequate prior treatment has been instituted.
    - Patients with hypersensitivity to dinoprostone or to any of the excipients listed in the SmPC for Propess/Prostin
    - Patients with placenta previa or unexplained vaginal bleeding during the current pregnancy.
    - Patients with evidence of any sign of infection, including genital tract infection

12 Recruitment

A total 327 normal risk nulliparous women will be recruited from the antenatal clinics in the hospital provided they fit inclusion criteria. There are approximately 3000 nulliparous women per annum attending the Rotunda Hospital who deliver at full term through any means. Breech presentation is present in approximately 160 cases within this cohort, giving an average pool of 2840 singleton cephalic nulliparous women to recruit from per year.

The study will be advertised through posters and media in the antenatal clinic waiting areas. The study may be advertised via the hospital website and social media pages. Additionally, medical staff will be aware of potential recruitment criteria and will be able to refer to study investigators if patients show an interest in taking part in the study. Patients who are eligible may be identified from the clinic lists via e-chart/iPIMS and contacted to assess interest if eligible.

12.1 Onsite Patient Contact Log

A patient screening log and patient enrolment log will be maintained at the trial centres. The screening log will detail the patient's full name, date of birth, hospital number and contact details for consented and screened patients. This log will be maintained locally and will not be sent outside the trial centre but may be monitored by authorised onsite personnel.

12.2 Screening Procedure

Participants will be identified from the antenatal clinic lists at the maternity site. A screening log will be maintained at the site for the purposes of monitoring eligibility and participation rates at site. Eligible women who consent to trial participation will have their details entered onto the Patient Enrolment Log which will identify the patients by a unique identification number.

Patient Information Leaflets will be issued to potential participants in the antenatal clinics. Monthly recruitment data, to include number of women eligible and number recruited, will be communicated to the Project Manager and will be reviewed together with the Principal Investigator and TSC.

Potentially eligible participants will be approached by the site investigator between 34-38 weeks' gestation, and will be given the patient information leaflet regarding the study. If interested they will then be invited to a consultation with a member of the research team at a dedicated antenatal clinic between 38+0 and 39+0 weeks' gestation. The study will be described, supplemented by written information, and eligible women will be invited to participate. Sufficient time for reflection will be allowed before written informed consent is obtained by the investigator. At this screening visit, a medical history will be recorded, and notes reviewed to ensure that the patient fulfils the inclusion criteria for study participation and that no exclusion criteria are met prior to randomisation.

13 Study procedures and schedule of assessments

13.1 Informed consent procedure

It is the responsibility of the Principal Investigator at the recruitment site, or another investigator delegated by the Principal Investigator to obtain written informed consent from each subject prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. “Adequate time” must be given for consideration by the patient before taking part.

The Investigator or designee will explain that patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason for withdrawal. No clinical trial procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into the trial.

A copy of the signed Informed Consent Form will be given to the participant. The original signed form will be retained in the Investigator Site File (ISF) at the study site and a copy placed in the medical notes.

If new safety information results in significant changes in the risk/benefit assessment, the patient information leaflet will be reviewed and updated if necessary and subjects will be provided with the new PIL in a timely manner and new consent obtained.

13.2 Randomisation procedures

A computer-generated randomisation sheet will be used to assign study participants to either Propess, Dilapan-S® 12 hours or Dilapan-S® 24 hours groups at Visit 1. The randomization sheet will provide notification of the treatment package to be assigned to the participant and a log of each randomisation will be retained. The randomisation will be performed by the study investigator providing the treatment. Subsequent to screening and consent procedures, the participants will be randomized to one of the three groups. The randomization will use a block size of 4 and the random number seed-generator and generating program will be retained for reproducibility. The software SAS 9.4 will be used to generate the randomization list.

13.3 Unblinding

Not applicable as this trial is open label.

13.4 Trial Visit Overview

a. Approach of potentially eligible participants will occur between 34+0 and 39+0) at which point the PIL will be distributed to interested parties.
b. Dedicated clinic visit (‘Visit 1’: Consent and screening) will occur between 38 and 39 weeks. Patients will be screened for inclusion and exclusion criteria and will be

offered to participate in the study. Informed consent will be obtained at this point in time, and a date & instructions for visit 2 given. Randomization will occur at this visit.

c. Visit 2 will occur between 39+0 and 39+4 and IOL will be commenced.
d. Visit 3 will occur within 11-28 hours of Visit 2.
e. Visit 4 (between 12 hours and 5 days of delivery), will be referred to as 'Delivery Visit'.
f. Visit 5 follow up will be conducted at 6 weeks post-partum (+/- 7 days)

1. Visit #	**1**	**2**	**3**	**4**	**5**
Visit Type	Screening & consent, Randomisation	Induction visit	Re-assessment Visit	Delivery Visit	Follow-up visit (or phone call/email/chart review)
Visit Timing	Between 38+0 & 39+0 weeks gestation	Between 39+0 and 39+4 weeks gestation	.First re-assessment within 11-28 hours of Visit 2 and subsequent re-assessments can be recorded if clinically indicated	Between 12 hours and 5 days of delivery date	6 weeks Postpartum (+/- 7 days
Informed Consent	X				
Screening Procedures					
Obtain relevant medical history *(including medication history)**	X				
Vital Signs *(include BP, Pulse, temperature, RR, O2 sats)*	X	X	X	X	
Urinalysis	X	X			
Bishop's Score		X	X		

Weight, Height and BMI	X[1]				
Ultrasound	X	X			
Physical examination *(only if symptom driven)*	X	X	X	X	
Abdominal examination	X	X	X		
Eligibility determination *(inclusion/exclusion assessment)*	X	X[2]			
Randomisation	X				
IMP administration		X[3]			
Participant safety checklist		X[4]			
Delivery details				X	
Maternal Satisfaction Questionnaire				X	X[5]
Neonatal outcomes[6]				X	X[7]
Adverse Events review		X	X	X	X
Concomitant Medication review	X	X	X	X	X
** This is assessed by a doctor on a case by case basis. Relevant medical issues would be inclusive of the systems disorders as in exclusion criteria. Non relevant medical issues may include, but are not limited to: anxiety/depression not requiring medications, history of urinary tract infections, past history of sexually transmitted infections that have been successfully treated, history of abnormal cervical smear tests, incidence of human papillomavirus, varicose veins, minor surgery or any surgery that would not result in contraindication to induction of labour)*					

1. ***If not already documented in the medical chart***
2. ***If Visit 1 & Visit 2 are not conducted on the same day, eligibility must be re-assessed***

3. ***After IMP is inserted, there will be a further CTG for 30-60 mins to ensure there are no signs of non-reassuring fetal testing before allowing the patient to return home. Patients will receive telephone calls from healthcare staff at approximately 8 hours and 14 hours post administration of IMP (Propess or Dilapan) to assess for maternal and fetal well-being. If patients do not answer, the healthcare staff will call the next of kin contact listed in the patient chart.***

4. ***Patients will be given a safety checklist prior to discharge home, and will be instructed to complete this checklist every 2 hours while at home. The checklist will include documenting the presence / absence of pains, fetal movements, rupture of membranes and vaginal bleeding every 2 hours. Patients will be given strict guidance on when to remove the Propess (if randomised to this arm), when to return to the hospital, including Instructions to return to the hospital in the event of spontaneous rupture of membranes, regular painful uterine contractions, increased frequency of uterine contractions, reduced fetal movements or vaginal bleeding (this will be outlined in the Patient Information Leaflet)***
5. ***Questionnaire will be posted to participants who did not receive it at Visit 4***
6. ***Birthweight & birthweight centile, apgar score at 1 minute, apgar score at 5 minutes, meconium staining noted, metabolic acidosis (defined as cord-artery pH < 7.05 with base deficit ≥ 12mmol/l), antibiotic use for suspected or confirmed neonatal infection, admission to neonatal unit, length of stay in neonatal unit in hours, neonatal mortality, shoulder dystocia.***
7. ***Neonatal outcomes are not required to be captured at Visit 5 if no change has occurred since Visit 4***

13.5 Baseline assessments

Baseline assessments at recruitment include:

- Obtain medical history
- Vital signs
- Physical examination (if symptom driven)
- Abdominal examination
- Weight, height, BMI
- Urinalysis
- Ultrasound
- Randomisation

Visit 2 assessments will include:

- Vital Signs
- Urinalysis
- Bishop's score
- Ultrasound
- Physical examination (if symptom driven)
- Abdominal examination
- IMP administration
- Adverse event review
- Concomitant medication review
- CTG

Visit 3 assessments will include:

- Vital Signs
- Bishop's score
- Physical examination (if symptom driven)
- Abdominal examination
- Adverse event review
- Concomitant medication review
- CTG

Visit 4 assessments will include:

- Vital Signs
- Physical examination (if symptom driven)
- Delivery details
- Maternal Satisfaction Questionnaire
- Neonatal outcomes
- Adverse event review
- Concomitant medication review

Visit 5 assessments will include:

- Maternal Satisfaction Questionnaire *(if unable to complete at Visit 4)*
- Neonatal outcomes (if there has been a change since Visit 4)
- Adverse event review
- Concomitant medication review

13.6 Treatment procedures

Propess will be administered vaginally at a standard dosing protocol, i.e. 1 device containing 10mg dinoprostone over 24 hours.
Dilapan-S® will be administered at a standard dosing protocol, i.e. the required number of rods intra-cervically over 24 hours.
Prostaglandin E2 will be administered if required at one 1mg dose vaginally 24 hours after the induction method has been inserted, at the discretion of the examining physician.

13.7 Subsequent assessments

N/A

13.8 Flowchart of study assessments

Assessment table of all procedures/tests/IMP administration will be completed at each visit.

13.9 Methods

13.9.1 Laboratory procedures

N/A

13.10 Definition of end of trial

The end of the trial will be defined as the 6 week post-partum consultation.

13.11 Discontinuation/withdrawal of participants and 'stopping rules'

Participants will be withdrawn from the trial if:

- There is evidence of any complications of pregnancy (e.g. PET) that deems the patient unsuitable for outpatient management.
- If it is deemed unsafe to allow the participant to return home once the IOL has commenced.
- Recording of any withdrawals will take place including the reason for withdrawal and the circumstances around the withdrawal.
- The trial will be stopped if there are any concerns for patient safety.

14 Name and description of all drugs or devices used in the trial

Propess Dinoprostone 10mg vaginal delivery system. The insert contains 10mg dinoprostone which is released over 24 hours.
Dilapan-S® is an osmotic hygroscopic dilator produced from a patented Aquacryl hydrogel.
Prostin is an intravaginal gel containing prostaglandin E2.

14.1 Treatment of subjects

Investigational product/treatment
Propess will be administered vaginally at a standard dosing protocol, i.e. 1 device containing 10mg dinoprostone over 24 hours. This is the standard dose for Propess as per manufacturer guideline and licencing.
Dilapan-Sâ will be administered at a standard dosing protocol, i.e. the required number of rods intra-cervically over 12 hours or 24 hours as per manufacturer guideline and licencing.

14.2 Concomitant medication

There are no specific concomitant medications that will restrict usage of these medications in this cohort of normal risk nulliparous women with no medical comorbidities requiring long term medications except for the use of herbal medications which might affect uterine contractions. However, if a patient is being treated for a medical condition such as essential hypertension/epilepsy/diabetes/moderate-severe asthma, and requiring any concomitant medications, this would be subject to our exclusion criteria as above, thus making the patient ineligible for the trial. Concomitant medications will be captured from Visit 2 until the 6 week post-partum follow up, with the exception of commonly used analgesia during the induction, labour and post-partum period such as paracetamol, NSAIDs, Oxynorm, and standard epidural related medications.

15 Investigational Medicinal Product

According to the definition of the EU clinical trial directive 2001/20/EC, an investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation, but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

15.1 Name and description of investigational medicinal product(s)

Name of the medication: PROPESS 10mg vaginal delivery system

Qualitative and quantitative composition: Each vaginal delivery system consists of a non-biodegradable polymeric drug delivery device containing 10mg dinoprostone (Prostaglandin E2) dispersed throughout its matrix
Pharmaceutical form: Vaginal delivery system

PROPESS is presented as a thin, flat semi-transparent polymeric vaginal delivery system which is rectangular in shape with rounded corners contained within a knitted polyester retrieval system.

Name of the medication: Dilapan-S®

Qualitative and quantitative composition is an osmotic hygroscopic dilator manufactured from an anisotropic xerogel of **Aquacryl®**, and comes in sterile, single use rods.

Pharmaceutical form: Dilapan-S® Dilapan-S® is classified as a CE marked medical device and contains no active pharmacological substance.

15.2 Name and description of each NIMP

Name of the medication: Prostin E2 Vaginal Gel 1 mg.

Qualitative and quantitative composition: Each 3 g gel (2.5 ml) syringe contains 1 mg dinoprostone.

Pharmaceutical form: Vaginal gel. Semi-translucent, thixotropic gel.

Prostin is being administered within its therapeutic indication as appropriate. It is not considered to be an investigational medicinal product for the purpose of this trial. At Visit 3, the administration of the Non-IMP Prostin (if necessary) will be captured in the participant medical record and this data will be used to inform the secondary outcome measure.

15.3 Summary of findings from non-clinical studies

The following are available from the SmPC forms for the relevant medications.

Propess 10mg vaginal delivery system

Preclinical studies have demonstrated that dinoprostone is a locally acting substance which is rapidly inactivated and thus it has no significant systemic toxicity.

The hydrogel and polyester polymers are inert compounds with good local tolerability.

Reproduction toxicity, genotoxic or carcinogenic effects of the polymers have not been investigated but systemic exposure is negligible.

15.4 Summary of findings from clinical studies

Overall, throughout the last years, all methods have been studied widely and have been repeatedly deemed safe methods of IOL. Known and acknowledged risks of both prostaglandin-based devices include the risk of uterine hyperstimulation with the potential to cause fetal heart rate abnormalities. Propess is a removable method, and studies have reported hyperstimulation can resolve with removal of the device.

Propess has been widely used, and thus the subject of many clinical trials in terms of efficacy and safety. Shirley (2018) published a review which outlines the efficacy and safety of the dinoprostone vaginal insert.

In terms of efficacy, studies as far back as 1992 have shown prostaglandin pessaries to be effective methods of cervical ripening[xiii],[xiv]. Risks of uterine tachysystole are acknowledged but multiple studies have shown reversal of this complication with removal of the pessary within 2-15 minutes. Tekin et al published a study in 2015 showing that Labour induction with Propess(®) is safe during both midwife-led and obstetrician-led labour management[xv].

In terms of outpatient IOL, a Cochrane review[iv] examined 4 published and unpublished randomized and quasi randomized trials with a combined total of 1,439 women. These trials assessed different methods of induction in the outpatient setting; thus, the results were not amalgamated. In those trials examined, vaginal PGE2 was used in two; and the outcomes showed no evidence of a difference in the women requiring instrumental delivery, with a similar rate of hospital stay in both groups. One study employed the use of a prostaglandin pessary in 300 women. There was no difference between groups for most review outcomes, including successful induction of labour. Mechanical induction with a Foley catheter was used in one study comprising 111 women. In this study there was no difference between groups.

Dilapan-S®

A prospective pilot study was carried out by Crosby et al[ix] in the National Maternity Hospital, Dublin who examined Propess and Dilapan-S® for use for inpatient IOL in the post-dates setting. This was a single-centre, prospective, observational pilot study (non-blinded / non-randomized) in which 52 women received either Dilapan-S® or Propess for IOL. The study found that Dilapan-S® was an acceptable, safe form of induction of labour in post-dates uncomplicated nulliparous pregnancy.

Recent studies have compared safety indices of balloon catheters with Dilapan-S® [vii] and found that Dilapan-S® is not inferior to the Foley Balloon for cervical ripening at term. Overall advantages of Dilapan-S® included FDA approval, the absence of anything protruding from the vagina, favourable safety profile, and the lack of applying tension to a Foley catheter needed for use, as well as patient satisfaction.

15.5 Summary of known and potential risks and benefits

As evidenced in the literature review, benefits of induction of labour include a reduced caesarean section rates, and a reduced maternal and neonatal morbidity rate. The specific stated risks of each modality involved in this study are stated below.

Propess 10mg vaginal delivery system

Benefits of Propess over other induction methods includce:
Reduction in frequency of vaginal examinations

Undesirable effects as per IMP SmPC

Summary of safety profile:

The most commonly reported adverse drug reactions in placebo-controlled and active comparator efficacy clinical trials (N=1116) were “fetal heart rate disorder” (6.9%), “uterine contractions abnormal” (6.2%) and “abnormal labour affecting foetus” (2.6 %).

The table below displays the main ADRs distributed by system organ classes (SOC) and frequency. Further, the ADRs seen during post-marketing experience are mentioned with unknown frequency.

Adverse reactions observed in clinical studies are presented according to their incidence, post authorisation reported adverse reactions are presented in the column frequency unknown.

System organ class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Not known: (cannot be estimated from the available data)**
Blood and lymphatic system disorders			Disseminated intravascular coagulation
Immune system disorders			Anaphylactic reaction Hypersensitivity
Nervous system disorders		Headache	
Cardiac disorders	Fetal heart rate disorder [1]*		
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders		Neonatal respiratory distress related conditions	
Gastrointestinal disorders			Abdominal pain, Nausea, vomiting, diarrhoea
Hepatobiliary disorders		Neonatal hyperbilirubinaemia	
Skin and subcutaneous tissue disorders		Pruritus	
Pregnancy, puerperium and perinatal conditions	Abnormal labour affecting fetus [2]* Uterine contractions abnormal Meconium in amniotic fluid Uterine tachysystole, uterine hyperstimulation, uterine hypertonus	Postpartum haemorrhage, Premature separation of placenta, Apgar score low Arrested labour Chorioamnionitis Uterine atony	Anaphylactoid syndrome of pregnancy Fetal distress syndrome [3]* Fetal, stillbirth, neonatal death [4]*
Reproductive system and breast disorders		Vulvovaginal burning sensation	Genital oedema
General disorders and administration site conditions		Febrile disorders	
Injury, poisoning and procedural complications			Uterine rupture

1* “Fetal heart rate disorder” was in clinical studies reported as “fetal heart rate abnormalities”, “fetal bradycardia”, “fetal tachycardia”, “unexplained absence of normal variability”, “fetal heart rate

decreased", "fetal heart rate deceleration", "early or late decelerations", "variable decelerations", "prolonged decelerations".

2* "Abnormal labour affecting fetus" as expression for hyperstimulation syndrome was in clinical studies reported as "uterine tachysystole" combined with "late decelerations", "fetal bradycardia", or "prolonged decelerations "

3* "Fetal distress syndrome" was also reported as "fetal acidosis" , "pathological CTG", "fetal heart rate abnormalities", "intrauterine hypoxia" or "threatening asphyxia". The term itself is unspecific, has a low positive predictive value and is often associated with an infant who is in good condition at birth.

4* "Fetal death, stillbirth, and neonatal death have been reported after application of dinoprostone, especially following the occurrence of serious events such as uterine rupture".

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard.

Dilapan-S®

The possible benefits of using Dilapan-S® over the current (mechanical and pharmacological) methods of induction include the following:

- Significant increase in cervical ripening and Bishop Score, which allows for the initiation of labour induction
- Minimal risk of uterine hyper-stimulation and impact on the fetal heart rate
- Effective and safe for women who have had a previous caesarean section
- No pharmacological side effects
- Gradual and predictable dilation due to its mode of action
- High maternal acceptability
- Accentuates the physiological processes of labour
- Efficiencies in midwifery care due to its one-time application (PGs usually require multiple administrations)
- Patented hydrogel ensures higher efficacy and predictability of effect in comparison to natural seaweed laminaria tents with less potential for reactivity or allergy.
- Certified production and non-porous synthetic material ensure higher safety in comparison to laminaria tents
- Easy application and storage in room temperature
- Sterile nature by design

Potential risks of using Dilapan-S® are:

- Rupture of membranes
- Vaginal bleeding from cervix, usually from the time of insertion as there can be trauma to the cervical tissue during the insertion process
- Allergic reaction from hypersensitivity to the components

- Contamination of the device during insertion
- Cervical laceration
- Vaso-vagal reaction from manipulation of the cervix
- Entrapment of the device
- Fragments of the device in the genital tract
- Retraction of the device into the uterine cavity

15.6 Description and justification of route of administration and dosage

Propess Administration:
A cardiotocograph tracing will be completed for 20 minutes prior to insertion of Propess®. A vaginal examination to determine the Bishop's score will be completed. Propess® will be administered using the standard dosing protocol, i.e. one device containing 10mg dinoprostone, releasing 0.3mg per hour over 24 hours as as per the manufacturer's guidelines in the SmPC as follows:

- Propess® should be removed from the freezer just prior to the insertion
- No thawing is required prior to use
- There is a "tear mark" on the side of the foil sachet
- Open the package along the tear mark across the top of the sachet
- Do not use scissors or other sharp objects which may cut the retrieval system
- Propess® should then be inserted high into the posterior vaginal fornix using only small amounts of water-soluble lubricants to aid insertion
- After Propess® has been inserted, the withdrawal tape may be cut with scissors always ensuring there is sufficient tape outside the vagina to allow removal
- No attempt should be made to tuck the end of the tape into the vagina as this may make retrieval more difficult
- The patient should be recumbent for 20 to 30 minutes after insertion

The patient will remain in the outpatient department for one hour post insertion to monitor for any side effects or uterine contractions, during which time 60 minutes of cardiotocograph tracing will be performed. If cardiotocograph testing is reassuring the patient will be allowed home. A safety checklist will be given to each patient to complete every 2 hours while at home. The patient will be advised upon leaving the hospital to return if she experiences any of the following:

- Spontaneous rupture of membranes
- Reduced fetal movements
- Constant abdominal pain
- Regular / painful uterine contractions
- Vaginal bleeding
- If the Propess® falls out

If Propess falls out post-insertion, the clinical staff will make a decision regarding the suitability of ARM, administration of Prostin to the subject, or administration of a new Propess. If the subject receives Prostin, they will be admitted to hospital and will not be discharged home. If Propess falls out before the protocol stipulated time period, this would not be considered to fit the category of need for second induction modality or failed induction.

The patient will be contacted via telephone call by a healthcare professional to assess for maternal and fetal wellbeing mid-afternoon (4pm) and evening (10pm) while the patient remains at home, based on

a presumed 8am insertion time. Patients will return to the hospital approximately 24 hours post insertion of Propess® for further evaluation of their labour progress. The vaginal delivery system should be removed after 24 hours irrespective of whether cervical ripening has been achieved. A dosing interval of at least 30 minutes is recommended for the sequential use of oxytocin following the removal of the vaginal delivery system.

Dilapan-S® administration:

A cardiotocograph will be completed for 20 minutes prior to insertion of Dilapan-S®. A vaginal examination to determine the Bishop's score will be completed. Dilapan-S® will be administered at a standard dosing protocol, i.e. the required number of rods intracervically over either 12 or 24 hours. Usually a set of 3–5 rods is required as per the manufacturer's guideline and licencing. Dilapan-S® rods will be administered as follows:

- A bivalve speculum should be inserted and the vagina and cervix should be prepared with an antiseptic solution
- Dilapan-S® should be removed from the package using a sterile technique
- The surface of Dilapan-S® can be lubricated using sterile water or saline prior to insertion
- Dilapan-S® should be inserted into the cervical canal gradually and without undue force
- It should traverse the external and internal cervical os
- Dilapan -S should not be inserted past the handle. The border of the knob/collar should rest at the external os
- More than one Dilapan-S® can be inserted into the cervical canal as deemed appropriate by the healthcare professional following clinical judgement of the risk / benefit ratio
- The patient should be recumbent for 20 minutes to 30 minutes after insertion

A cardiotocograph will be completed in the outpatient's setting for 20-40 minutes post- insertion of Dilapan-S®. If cardiotocograph testing is reassuring the patient will be allowed home. The patient will be advised upon leaving the hospital to return if she experiences any of the following:

- Spontaneous rupture of membranes
- Reduced fetal movements
- Constant abdominal pain
- Regular / painful uterine contractions
- Vaginal bleeding
- If the Dilapan-S® rods fall out

If Dilapan-S® falls out after an hour post-insertion, the clinical staff will make a decision regarding the suitability of ARM, administration of Prostin to the subject, or insertion of new Dilapan. If the subject receives Prostin, they will be admitted to hospital and will not be discharged home. If Dilapan falls out before the protocol stipulated time-period, this would not be considered to fit the category of need for second induction modality or failed induction.

15.7 Dosages, dosage modifications and method of administration

There are no dose adjustments to the above regime.

Dilapan-S® will involve the insertion of the required number of rods as per the manufacturers instruction.

15.8 Preparation and labelling of Investigational Medicinal Product

Preparation and labelling of the investigational medicinal products should be completed in accordance with the Annex 13 guidelines.

15.9 Drug accountability

Master inventory logs of the IMP will be held in the site pharmacy to allow for traceability of the IMP. Shipment records or delivery documents will be in the site pharmacy and recorded in the log. Each patient will have a dispensed and returned accountability log.

Drug accountability logs will be kept in the pharmacy file at the study site and will be signed off at the end of the trial.

After site visits by the study monitor, returned IMP will be destroyed according to the local hospital destruction policy.

15.10 Source of IMPs

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

- Propess
- Dilapan-S®

15.11 Dose modifications

There are no dose modifications or deviations from the above specifications for this study.

15.12 Assessment of compliance

Compliance with medication is not applicable as administration of both IMPs are performed within a clinical setting by the treating investigator.

15.13 Post-trial IMP arrangements

There will be no arrangements to provide the IMPs to trial participants post trial as this study is specific to IOL.

16 Recording and reporting of adverse events and reactions

16.1 Definitions

Term	Definition
Safety Definitions for Propess Events	
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
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. *This includes medication errors, uses outside of protocol (including misuse and abuse of product)*
Serious adverse event (SAE)	Any adverse event that: • results in death, • is life-threatening, • requires hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect • Important Medical Event*
**These events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered 'serious'*	
Serious Adverse Reaction (SAR)	Events that meet the criteria of an SAE and a causal relationship between the investigational medicinal product and the event cannot be ruled out
SUSAR	Suspected Unexpected Serious Adverse Reaction A serious adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out: (a) in the case of a product with a marketing authorization, in the summary of product characteristics for that product, (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.
• **Safety Definitions for Dilapan-S® Events**	
Adverse Device Effect (ADE)	All untoward and unintended responses to the medical device. The phrase "responses to a medical device" means that a causal relationship between the device under investigation and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
Serious Adverse Device Effect (SADE)	A serious adverse device effect (SADE) is any untoward medical occurrence seen in a patient that can be attributed wholly or partly to the device which resulted in any of the characteristics or led to characteristics of a serious adverse event as outlined above.

	SADE is also any event that may have led to these consequences if suitable action had not been taken or intervention had not been made or if circumstances have been less opportune.

16.2 Safety Event Recording

All Adverse Events (AEs) occurring during the study observed by the investigator or reported by the subject will be recorded on the CRF, except for those events that meet the definition of a non-reportable event. All AEs will be recorded from Visit 2 until the 6 weeks postpartum follow up visit

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to the study medication, other suspect medication or device and action taken and outcome. Follow-up information should be provided as necessary. All AEs will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

If the investigator suspects that the subjects' disease has progressed faster due to the administration of the IMP, then he will record and report this as an unexpected adverse event. It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the subject's removal from treatment. A subject may also voluntarily withdraw from treatment due to what she perceives as an intolerable AE. If either of these occurs, the subject must undergo an end-of-study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

16.3 Assessments of AEs

Each AE will be assessed for the following criteria:

16.3.1 Severity

Category	Definition
Mild	The AE does not interfere with the volunteer's daily routine, and does not require intervention; it causes slight discomfort
Moderate	The AE interferes with some aspects of the volunteer's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	The AE results in alteration, discomfort or disability which is clearly damaging to health

16.3.2 Causality

- The assessment of relationship of all events to the administration of Propess or Dilapan-S® is a clinical decision based on all available information at the time of the completion of the case report form. The following categories will be used to define the causality of events.

Category	Definition
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 (e.g. 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 patient's clinical condition, other concomitant treatments).
Not related*	There is no evidence of any causal relationship.
Not Assessable*	Unable to assess on information available.

16.3.3 Expectedness

Category	Definition
Expected	An adverse event that is classed in nature as serious and which is consistent with the information about the IMP listed in the Investigator Brochure (or SmPC if Licensed IMP) **or clearly defined in this protocol.**
Unexpected	An adverse event that is classed in nature as serious and which is not consistent with the information about the IMP listed in the Investigator Brochure (or SmPC if Licensed IMP)

The reference document to be used by the Study Coordinator to assess expectedness of the event against the IMP. The reference documents are the SmPC for Propess and the Dilapan-S® excerption of instructions for use.

16.3.4 Seriousness

The Investigator should make an assessment of seriousness as defined in section 16.1.

Collection, recording and reporting of adverse events to the Study Coordinator (RCSI) will be completed according to the RCSI Expedited Safety Reporting SOP.

16.4 Procedures for reporting SAEs

All Serious Adverse Events (SAEs) will be reported to RCSI Pharmacovigilance, except for those events that meet the definition of a non-reportable event. The Principal Investigator (PI) or appropriate designee is responsible for capturing all SAEs on appropriate trial specific forms, and reporting to RCSI Pharmacovigilance (Pharmacovigilance@rcsi.ie) within 24 hours of first becoming aware of the event *(as per the RCSI SOP on Expedited Safety Reporting).*

As outlined in Section 16.3, SAEs will be collected from Visit 2 until the 6 weeks postpartum consultation and will be followed until resolution or until stabilized with sequelae.

Regarding AE/SAE in the baby, all NICU admissions will be captured as adverse events, with investigators assessing each admission to verify if it meets criteria for a SAE. All AEs that meet SAE criteria will also be recorded as such as per protocol. The following events that require admission to the NICU will not be recorded as SAEs:

- NICU admission for work-up for infection
- Transient tachypnoea of the newborn
- Observation due to slow transition at birth
- Admission for jaundice requiring phototherapy (Jaundice not requiring phototherapy will be non-reportable).

The following are a list of non-reportable events that are considered to be pregnancy or induction-related. These events will not be recorded as adverse events for the purpose of this trial:

- Hospitalisation for labour and delivery
- Pelvic girdle dysfunction
- Indigestion
- Fatigue
- Constipation
- Shortness of breath
- Urinary frequency/ nocturia
- Migraine and tension headache
- Nosebleeds and bleeding gums
- Varicose veins
- Haemorrhoids
- Nausea and vomiting
- Labour or induction related pain
- Rash unrelated to the induction medium
- Back pain or sciatica
- Palpitations
- Carpal tunnel syndrome
- Bilateral oedema of feet/legs/hands
- Fetal normal variants on ultrasound: Pyelectasis, choroid plexus cysts, echogenic intracardiac focus
- Due to breast feeding issues or need for emotional support

- Due to blood pressure control issues
- Due to shortness of breath
- Due to ante-partum haemorrhage
- Due to secondary post-partum haemorrhage
- Due to the need for antibiotics for a delivery related infection
- Infections unrelated to labour and delivery e.g. Urinary tract infection, Mastitis/Breast abscess, Respiratory tract infection, cellulitis not related to wound site, COVID related admissions.
- Due to concerns regarding baby including previously undiagnosed anomalies, weight gain or issues unrelated to labour and delivery.
- Due to dehydration or vitals affected by dehydration (e.g. maternal tachycardia).
- Abnormal vital signs during and within 4 hours pre and post labour and delivery (e.g. tachycardia, hypotension, hypertension)
- Anaemia not requiring blood transfusion
- Neonatal jaundice not requiring admission to NICU or treatment
- Neonatal review not requiring NICU admission
- Any pre-existing anomaly in the baby that was previously undiagnosed but unrelated to labour and delivery.

16.4.1 Notification of deaths

All deaths, including deaths deemed unrelated to the IMP will be reported to the Study Coordinator as a serious adverse event (please see Section 16).

16.4.2 Reporting SUSARs

The Study Coordinator, RCSI will notify the main REC and competent authority of all SUSARs. SUSARs that are fatal or life-threatening must be notified to the CA and REC within 7 calendar days after the Study Coordinator has learned of them. Other SUSARs must be reported to the REC and CA within 15 calendar days after the Study Coordinator has learned of them.

16.4.3 Development Safety Update Reports

The Study Coordinator, RCSI will provide the main REC and the competent authority with Development Safety Update Reports (DSUR) which will be written in conjunction with the trial team and the RCSI Sponsorship office. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

16.4.4 Overdose

The study devices will be used as per protocol, administered by a study investigator. Therefore there are no opportunities for an overdose to happen.

16.4.5 Reporting Urgent Safety Measures

If any urgent safety measures are taken the PI/Study Coordinator shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the competent authority and the relevant REC of the measures taken and the circumstances giving rise to those measures.

16.4.6 Notification of Serious Breaches to GCP and/or the protocol

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 subjects of the trial; or

(b) the scientific value of the trial.

The Study Coordinator of the clinical trial shall notify the competent authority in writing of any serious breach of –

(a) the conditions and principles of GCP in connection with that trial; or (b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

The Study Coordinator will be notified immediately of any case where the above definition applies during the trial conduct phase. The Study Coordinator's SOP on the 'Notification of violations, urgent safety measures and serious breaches' will be followed.

17 Data management and quality assurance

17.1 Confidentiality

All data will be handled in accordance with the applicable Data Protection legislation

The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data.

The subject date of birth and trial identification number, will be used for identification.

17.2 Data collection tools and source document identification

Data will be entered prospectively at the time of the visits into the patient's electronic chart (source data) as is standard protocol within the hospital. All data will be collected by a member of the team from the electronic chart or filled questionnaires and entered into the CRF.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

For data where no prior record exists and which are recorded directly in the eCRF, the eCRF will be considered the source document, unless otherwise indicated by the investigator.

In addition to the above, date(s) of conducting informed consent, trial number, study arm and the fact that the patient is participating in a clinical trial should be added to the patients' medical record contemporaneously.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

17.3 Data handling and analysis

Data handling will be in accordance with Data Protection Legislation. The study coordinator will be the Data Controller and will ensure data security, privacy (anonymization) and archival, in accordance with the Hospital IT department data handling policies. The study data will be stored in a centralized and secured area and will not be distributed to a third party. The study data will only be accessed by study personnel, as required, for data monitoring and data analysis.

The software STATA 16 ICE will be used for data entry using pre-specified fields. In addition, the SAS Version 9.4 software will be used for querying data (anomaly detection and rectification), for DSMB reporting and for statistical analysis at study completion. A detailed Statistical Analysis Plan (SAP) will be finalised prior to last-patient last-visit.

18 Record keeping and archiving

Archiving will be authorised by the Study Coordinator following submission of the end of study report. The principle investigator is responsible for archiving the investigator site file. All essential documents will be archived for a minimum of 5 years after completion of trial. Destruction of essential documents will require authorisation from the Study Coordinator.

19 Statistical Considerations

19.1 Outcomes

19.1.1 Primary outcomes

The primary outcome will be the overall vaginal delivery (VD) rate.

Related outcomes, such as VD rate within 36 hours and 48 hours, will be considered secondary.

19.1.2 Secondary outcomes

The following secondary outcomes will be compared:

1. Overall change in Bishop score before and after cervical ripening
2. Rates of vaginal delivery at 36 hours after insertion of either Propess or Dilapan-S®
3. Rates of vaginal delivery at 48 hours after insertion of either Propess or Dilapan-S®
4. The need for second induction modality
5. Rates of hyper-stimulation *
6. Rate of failed induction
7. Overall length of stay in hospital
8. Rates of adverse neonatal outcome
9. Rates of adverse maternal outcomes
10. Maternal satisfaction scores with the outpatient induction process
11. Caesarean delivery rates, categorized by “overall rate”, “rate for failure to progress/failed induction”, and “rate for non-reassuring fetal testing”
12. Analgesia use in each group, including rates of epidural

13. Compare rates of 39 weeks' successful vaginal delivery in the outpatient setting to rates of successful vaginal delivery in the inpatient setting. **

**defined as more than 7 contractions in a 15 minute time period persistently for more than 30 minutes and requiring a medical intervention (such as a clinical decision to remove the Propess/Dilapan or administer a medication such as Terbutaline).*

***defined as a group of low risk nulliparous women who did not undertake elective induction of labour at 39 weeks as part of this trial.*

19.2 Sample size and recruitment

19.2.1 Sample size calculation

A single primary comparison will be used to determine efficacy. The sample size was therefore revised, from a potentially under-powered study of two co-primary comparisons, to an adequately powered study of a single primary comparison.

A 10% margin was used as the non-inferiority margin for the treatment comparison of Dilapan-S (combined groups) versus Propess. SVD rates were assumed to be 70%, 75% and 80% in the Propess, Dilapan-S® (24 hours) and Dilapan-S® (12 hours) groups, respectively. Assuming 90% statistical power, a one-sided 2.5% level of statistical significance and equal treatment group allocation, the study sample size required is 285 for a per-protocol analysis. Allowing for a 15% non-adherence rate, the total required recruitment is 327 (109 per group) for the intention-to-treat analysis. Other treatment comparisons will be considered secondary and exploratory.

19.2.2 Planned recruitment rate

There are approximately 3000 eligible patients per year attending the Rotunda as published annually in the hospital reports. Similar trials in the past have shown an uptake rate of 30% for inpatient induction of labour. With a more conservative uptake rate of about 20% (3000 x 20%=600), we would therefore expect to recruit the required number of participants within 30 months (recruitment will have a maximum allowable duration of 30 months), allowing for dropout rates and those that fit exclusion criteria.

19.3 Statistical analysis plan

19.3.1 Summary of baseline data and flow of patients

All baseline and follow-up data will be presented using summary statistics and graphs (consort diagram, histograms, scatterplots, box-plot) according to study treatment group and study analysis population. A detailed Statistical Analysis Plan will be finalized prior to last-patient-last-visit.

19.3.2 Primary outcome analysis

The analysis of the primary outcome will use a confidence interval (95% level of confidence) for simple differences in proportions. Non-inferiority will be determined on the lower confidence interval limit (equivalent to a one-sided 97.5% confidence interval). Conditional on non-inferiority being demonstrated, superiority will be determined. The analyses will be performed in the per-protocol population, supported by an intention-to-treat analysis.

19.3.3 Secondary outcome analysis

Secondary outcomes will be compared using confidence intervals and hypothesis tests. However, these will be considered exploratory in nature. No adjustment for multiple testing will be performed.

19.3.4 Sensitivity and other planned analyses

Multiple (multivariate) logistic regression for the primary endpoints to adjust for potential prognostic variables will be performed. Such analysis will be deemed exploratory in nature and not considered the primary analysis.

19.4 Randomisation methods

Patients will be randomized using simple random allocation to either Dilapan-S® (12-hour insertion or 24-hour insertion) or Propess in a 1:1:1 ratio using a block size of 6 via a computer-generated randomization procedure (software SAS Version 6.4).

19.5 Interim analysis

No interim analysis will be performed.

19.6 Other statistical considerations

Missing data mechanisms will be explored with respect MNAR (missing not at random) and potential mechanisms associated will assessment biases will be explored statistically.

20 Name of Committees involved in trial

The Chief Investigator (CI) will be responsible for selecting the members of the Trial Management Group (TMG), Trial Steering Committee (TSC) and Data Safety Monitoring Board (DSMB). The CI will organise the structure, frequency and agenda of meetings. A member of the Study Coordinator office (RCSI) will sit on the TMG to provide advice and maintain trial oversight. The terms of reference for the TMG, TSC and DSMB will be developed by the Investigator and the Study Coordinator and will be reviewed by the Study Coordinator prior to final approval to ensure they meet the requirements.

Trial Management Group (TMG):
The Trial Management Group will meet two-monthly and be responsible for the day-to-day management of the trial and include the PI, a Study Coordinator representative collaborators, statistician, trial manager and research assistants. The TMG will monitor all aspects of the conduct and

progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

The TMG will report to the TSC and will ensure that the study is conducted in compliance with the protocol, GCP and applicable regulations. The responsibilities will include (but are not limited to):

- Reporting to the Trial Steering Committee
- Identification of trial sites
- Confirmation that all approvals are in place before release of the IMP and the start of the trial at site
- Provision of training about the trial at site
- Provision of trial materials to the site
- Establishment of a data management centre
- 24-hour advisory support
- Provision of regular information about the progress of the study to collaborators
- Response to any questions (e.g. from collaborators) about the trial
- Data security and quality and observation of data protection laws
- Safety reporting
- Assurance that trial is conducted in accordance with the ICH GCP
- Statistical analysis
- Publication of trial results

Data Safety Monitoring Board (DSMB):

The outcome objective of the DSMB is to provide impartial and objective assessment of clinical trial safety data. Independence of the DSMB promotes:

- Greater objectivity relative to overall clinical benefit risk assessment
- Increased credibility of the clinical trial data
- Enables modification to trial, where necessary, in response to new external DSMB recommendation without introducing bias.

The independent DSMB members will review clinical trial data to evaluate safety and scientific validity of the clinical trial. Review of the full safety data from the clinical trial will enable impartial conclusion and recommendation which may be to do one of the following:

- Continue with the clinical trial as planned
- Continue with the clinical trial but amend the protocol prior to moving to next phase of clinical trial
- Stop the clinical trial

Trial Steering Committee (TSC):

The TSC is an independent body whose members do not have a role in running the clinical trial. For the purpose of this Trial, the TSC will be comprised of the TMG members with the addition of one independent person and will meet at a frequency outlined in the terms of reference. The role of the TSC is to oversee and supervise the progress of the clinical trial and ensure the clinical trial is being

conducted in accordance with GCP and applicable regulations. The TSC will agree to any protocol amendments and provide advice to the CI on all aspects of the clinical trial. The TSC will make major decisions regarding the continuation of the clinical trial or substantial amendments to the protocol based on the recommendations of the DSMB and ethics committee. The responsibilities of the TSC will be documented in the Terms of Reference.

The terms of reference for these committees will need to be provided in separate documents

21 Direct Access to Source Data/Documents

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.

22 Ethics and regulatory requirements

The Study Coordinator will ensure that the trial protocol, patient information leaflet, informed consent form, GP letter and submitted supporting documents have been approved by the appropriate competent authority and a research ethics committee, prior to any patient recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation.

Before the site can enrol patients into the trial, the Principal Investigator or designee must apply to the hospital for permission to conduct the study and be granted written permission. It is the responsibility of the Chief Investigator/ Principal Investigator or designee at site to ensure that all subsequent amendments gain the necessary approval. 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 16.4.5 for reporting urgent safety measures).

Within 90 days after the end of the trial, the CI/Study Coordinator will ensure that the main REC and the competent authority is 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.

23 Monitoring requirement for the trial

The Study Coordinator, RCSI will assign an independent monitor who will visit the investigator intermittently to validate compliance of the protocol to GCP, the maintenance of the study related records, and the extensiveness and accuracy of a proportion of CRF entries compared to source data. The investigator will co-operate with the monitor to ensure that any potential discrepancies are resolved.
Monitoring procedures include a site initiation visit designed to clarify all prerequisites before the trial commences at the site, interim site monitoring visits and study close-out visits. The study will be monitored by regular scheduled visits to site and on-going communication via telephone and e-mail.

During site visits the monitor will review; original patient records for the patient group; CRFs; drug accountability records; investigator site file and document retention. Study procedures will be observed by the monitor and any issues will be discussed with the PI or designee as necessary.
At a minimum, source documentation will be available to substantiate subject identification, eligibility, and participation; proper informed consent procedures; dates of visits; adherence to protocol procedures; records of safety and efficacy parameters; adequate reporting and follow-up of AEs; administration of concomitant medication; drug receipt/dispensing/return records; study drug administration information; and dates of subject completion, discontinuation from treatment, or withdrawal from the study, including the reason if appropriate.
CRF entries will be verified with the source documentation, if applicable (in some cases there are no source pages, therefore verification is not necessary). If any data, signatures, or forms are missing or incorrect, the Investigator or designee will be informed and corrections will be made. Direct access to all source documents must be guaranteed by the PI, who must provide support at all times for these activities.

24 Finance

Funding for this study has been obtained through The Rotunda Foundation (Charity Registration CHY20091) and Medicem Technology s.r.o.

25 Insurance

The Rotunda Hospital (Sponsor) will indemnify claims from participants for injury caused by their participation in the clinical trial. However, as this clinical trial is being carried out at a hospital site, the hospital will continue to have a duty of care to the participants of the clinical trial.

26 Publication policy

All proposed publications will be discussed with the Study Coordinator, RCSI prior to publishing other than those presented at scientific forums/meetings. Please refer to the RCSI publication policy.

27 Statement of compliance

The trial will be conducted in compliance with the approved protocol, the ROI Regulations, ICH GCP and the applicable regulatory requirement(s).

28 Appendices

Appendix 1: Instructions for use for Dilapan-S®
Appendix 2: SmPC for Propess
Appendix 3: RCSI Expedited Safety Reporting SOP
Appendix 4: IMP Labels
Appendix 5: Maternal Induction of Labour Questionnaire

29 References

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Summary of changes made from first to final protocol:

Protocol Version & Date:

- Version 1.0: 13-Jul-2020
    - Revisions based on HPRA review of protocol version 1 dated 30-Apr-2020 and requests. (Objectives, eligibility, schedule of assessments, IMP and safety sections revised).
- Version 2.0: 23-Nov-2020
    - Amended wording of primary objective.
    - Clarity provided for exclusion criteria.
    - Procedure for Propess & Dilapan administration clarified.
    - Removal of typo "placebo".
    - Non-reportable AEs added to safety section
- Version 2.0 Addendum: 11-Jan-2021
    - Removal of the following non-reportable AEs from protocol V2 23-Nov-2020:
        - 1. Failure to progress in labour
        - 2. Non-reassuring fetal heart rate tracings during labour
        - 3. Obstetric need for cesarean delivery, forceps-assisted delivery, vacuum-assisted delivery, or episiotomy
        - *Note: Upon HPRA review, the above AEs were removed from the non-reportable list, for continued careful monitoring of potential adverse outcomes and rigorous safety monitoring throughout the trial.*
- Version 3.0: 19-Feb-2021
    - Clarity added around timeframe in exclusion criteria.
    - Addition of non-reportable concomitant medications.
    - Footnote added to schedule of assessments to allow partner of trial subjects to receive safety phone call if unable to contact primary patient phone.
- Version 4.0: 01-Oct-2021
    - Additional site and contact details added:
        - *Note: In October 2021 the option for expansion to The National Maternity Hospital as an additional site was under discussion, and protocol amended to reflect same.*
        - Recruitment numbers updated to reflect second site
    - Visit 5 amended to allow for phone or chart review follow up.
    - Visit 3 timeframe amended.
    - Footnotes added to schedule of assessments for clarity on procedures.
    - Addition of non-reportable AE of "infections unrelated to labour and delivery".
- Version 5.0: 28-Nov-2022
    - Removal of National Maternity Hospital as a site and corresponding National Maternity Hospital PI details.
    - Trial duration changed from 24 to 30 months to allow for additional recruitment time.
    - Certain contact details deleted and other details corrected.
    - Clarity provided in the inclusion criteria around what are considered relevant medical issues that would be considered when assessing eligibility. Wording added also to outline that this is assessed on a case by case basis.
    - Clarity provided in the exclusion criteria that known maternal health problems that would directly affect the risk status of the woman are exclusionary. Wording added also to outline that this is assessed on a case by case basis
    - Potential risks updated based on revisions to Section 4.8 of the Propess SmPC. Typo corrected “tocolytics”.

- Statistician revised primary and secondary objectives and outcome measures, sample size (reduced from 465 to 327).
- Footnote added to provide clarity on what is considered to be relevant and non-relevant medical history.
- Wording added in footnote #6 of table of assessments to state length of stay in the neonatal unit will be captured in hours.
- Wording amended to allow for scenario where Propess or Dilapan falls out.
- Section added regarding new-born NICU admissions that are to be captured as adverse events. Non-reportable adverse events for the new-born were added.

HOME INDUCTION Trial
Statistical Analysis Plan

Contents

2. Introduction

As per standard reporting of randomized controlled trials (ICH E9, CONSORT), all collected outcome data will be presented in statistical tables, according to treatment group, in addition to patient listings generated for subsets of particular interest (e.g. patient withdrawals, serious adverse drug reactions). The statistical methods (below) are consistent with the trial protocol descriptions.

All baseline and follow-up data will be presented using summary statistics and graphs (consort diagram, histograms, scatterplots, box-plots) according to study treatment groups and to analysis population.

3. Data Handling and Analysis

Data handling will be in accordance with Data Protection Legislation. The study coordinator will be the Data Controller and will ensure data security, privacy (anonymization) and archival, in accordance with the Hospital department (RCSI) data handling policies.

The study data will be entered in a centralized database (CLININFO®), exported and secured on the RCSI network. The data will not be distributed to a third party. The study data will only be accessed by study personnel, as required, for data monitoring and data analysis.

All study outcomes entered on the database will be checked for completeness and correctness (data anomalies). The centralized database (CLININFO®) will then be closed.

SAS Version 9.4 software will be used for querying data and for statistical analysis.

4. Study Outcomes

For all study participants, information will be recorded in the electronic medical record (EMR) as is standard for all patients in the hospital. Data on the primary and secondary objectives will be collected and collated. At the initiation of induction of labor, the gestational age and exact time of initiation of induction (placement of investigational medicinal product [IMP]) will be recorded. A questionnaire will be given to participants to complete during their postnatal admission in the first feasible instance following delivery in order to assess their satisfaction scores with the process of outpatient induction.

4.1 Primary Outcome Measure

The primary outcome measure will be (overall) vaginal delivery. This comprises both operative vaginal delivery (OVD) and spontaneous vaginal delivery (SVD), at any time.

Operative vaginal delivery means either vacuum-assisted or forceps-assisted vaginal delivery. Spontaneous vaginal delivery means vaginal delivery without the need for vacuum or forceps assistance.

4.2 Secondary Outcome Measures

The following secondary outcome measures will be assessed. As these are secondary outcomes, they may be updated or explored in greater detail, as considered reasonable.

1. Overall change in Bishop score before and after cervical ripening
2. Rates of vaginal delivery at 36 hours after insertion of either Propess or Dilapan
3. Rates of vaginal delivery at 48 hours after insertion of either Propess or Dilapan
4. The need for second induction modality
5. Rates of hyperstimulation
6. Rates of failed induction
7. Overall length of stay in hospital
8. Rates of adverse neonatal outcomes
9. Rates of adverse maternal outcomes
10. Maternal satisfaction scores with the outpatient induction process
11. Cesarean delivery rates, categorized by “overall rate”, “rate for failure to progress/failed induction”, and “rate for non-reassuring fetal testing”
12. Analgesia use in each group, including rates of epidural
13. Compare rates of 39 weeks’ successful vaginal delivery in the outpatient setting to published rates of successful vaginal delivery in the inpatient setting and to those (inpatient) who were eligible but did not consent to participate in the clinical trial (separate ethics approval provided).

The primary objective will therefore assess the efficacy of achieving labor with each of the study induction methods. The secondary objectives will assess other efficacy measures, safety measures and maternal satisfaction scores.

5. Analysis Populations

Three analysis populations are specified and these are defined as:

Intention-to-treat (ITT): All patients who are randomized to a treatment arm, with the primary outcome recorded, irrespective of whether or not the patient actually received the IMP. Study participants with withdrawal of consent (of participation and a request for removal of data) will necessarily be excluded.

Safety Population: Patients who are randomized but analysed according to actual treatment received.

Per-protocol (PP): As per the intention-to-treat population but only including those having receiving the randomized treatment, and excluding withdrawals from the study. No further exclusions from the PP population will be made, as is recommended for non-inferiority trials to avoid selection biases.

Subgroups of the ITT or PP populations will be analyzed if considered clinically important and any protocol deviations will be explored.

6. Study Endpoints

6.1 Primary Endpoint

To demonstrate non-inferiority in the efficacy of Dilapan (12 hours or 24 hours insertion) to Propess for outpatient induction of labor at 39 weeks' gestation in otherwise uncomplicated, normal-risk nulliparous women.

The determination of non-inferiority, using a 10% margin, will be made using a 95% confidence interval for a difference in proportions (i.e. the lower 2.5% bound of the confidence interval).

6.2 Secondary Endpoints

1) To compare the Dilapan (12 hour) group to the Propess group in the primary endpoint and secondary endpoints

2) To compare the Dilapan (24 hour) group to the Propess group in the primary endpoint and secondary endpoints

3) To compare the Dilapan (12 hour) group to the Dilapan (24 hour) group in the primary endpoint and secondary endpoints

4) To compare Dilapan 12-hour, Dilapan 24-hour and Propess at 36 hours and 48 hours respectively from insertion time to delivery

Similar, to the primary endpoint, the secondary endpoints will be compared using confidence intervals. However, the study is not powered to determine non-inferiority (or superiority) for these secondary comparisons.

7. Statistical Analysis

7.1 Primary Outcome Analysis

The analysis of the primary outcome will use a confidence interval (95% level of confidence) for simple differences in proportions. Wald-type confidence intervals will be used, provided they are consistent with other methods. Non-inferiority will be determined on the lower confidence interval limit (equivalent to a one-sided 97.5%

confidence interval). Conditional on non-inferiority being demonstrated, superiority will be determined. The analysis will be performed in the per-protocol population, supported also by an intention-to-treat analysis.

7.2 Secondary Outcome analysis

Secondary outcomes will be compared using confidence intervals and hypothesis tests (p-values). However, these will be considered exploratory in nature. No adjustment for multiple testing will be performed.

7.3 Sensitivity and Other Planned Analyses

Multiple (multivariate) logistic regression for the study endpoints to adjust for potential prognostic variables will be performed. Specifically, maternal age and BMI will be explored in terms of how they might influence vaginal delivery rates. Such analyses will be deemed exploratory in nature.

7.4 Other Statistical Considerations

Missing data mechanisms will be explored with respect to MNAR (missing not at random), if such missing data is considerable.

Appendix: Table Template

Primary Study Endpoint (Per-protocol population)

Outcome	**Dilapan-12 (N=)**	**Dilapan-24 (N=)**	**All Dilapan [A] (N=)**	**Propess [B] (N=)**	**Difference [A-B] (95% CI)#**
Vaginal delivery	*n(%)*	*n(%)*	*n(%)*	*n(%)*	*x% (y% - z%)*

Wald asymptotic confidence limits without continuity correction.