SOLVE TRIAL PROTOCOL

A randomised controlled trial of a Synthetic Osmotic cervical dilator for induction of Labour in comparison to dinoprostone Vaginal insErt:

the SOLVE trial

Version 7.0 04.12.2019

Sponsor: Birmingham Women's and Children's NHS Foundation Trust

Chief Investigator: Prof Janesh Gupta, M.D., FRCOG

Coordinating Unit: Birmingham Clinical Trials Unit, University of Birmingham

Funder: Medicem Technology S.R.O, Vinohradska 1511/230, Prague 10, Czech Republic (www.medicem.com)

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Data Monitoring Committee (DMC)

Independent members:	Dr Andrew Weeks (Chair). Prof Ben Mol (Independent member – Obs/Gynae) Dr Pat Yudkin (Independent member – Statistician)

Protocol development and sign off

Protocol Amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

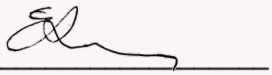
Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
N/A	10/2/17	2.0	Response to original REC	Clarification on repeat doses (section 6.3.1-2) Addition of informing GP (section 5.4) Clarification on withdrawal (section 6.6.1) Schema version number update Power calculations corrected (section 12.2.4)
AM01 & AM02	13/10/17	3.0	Substantial	Specific definition of secondary objective (Section 2.2) Definition of eligibility criteria for pragmatic implementation of the trial (Section 4) Removal of two minimisation criteria (section 5.6.1) Clarity around Blinding (Section 5.8) Clarity around dosing schedule (Section 6.3) Specific definition of outcome measures (Section 7.2-7.6) Clearer definition of end of trial (Section 11) Clarity on analysis of outcome measures (Section 12.2) Specify the funder (Section 13.1) Update SmPC PROPESS (Appendix 3) Update on TMG information (Page 2) Addition of sites (AM02 minor)
AM03 & AM04	20/4/18	4.0	Substantial	Removal of Bishop Score from eligibility criteria (section 4) Removal of USS scan dates from eligibility criteria (section 4) Addition of table of responsibilities (appendix) Addition of email address for SAEs (front pages)

				Merger of HEFT and UHB Trusts
N/A	21/5/18	5.0	Non-substantial, Non-reportable	Change over to General Data Protection Regulations.
AM05	02/08/2018	6.0	Substantial	Amendment to DILAPAN-S dosing schedule (Section 6.3) Removal of the need for CTG monitoring (Section 6.3.1 and Section 6.3.2) Removal of the use of iodine for cervical cleansing (Section 6.3.1) Amendment to Discontinuation of intervention (Section 6.6) Amendment to Withdrawal and re-confirmation of consent (Section 6.8) Addition of definitions of reportable SAEs and protocol-exempt SAEs not requiring reporting on a SAE form (Section 8) Removal of Sections 7.4-7.6 regarding CRF completion as these conflicted with Section 9. Inclusion of Investigators Brochure for Dilapan-S (Appendix 6) Minor typographical admendments and points of clarification
AM09	27/11/2019	7.0	Substantial	Minor typographical revisions throughout. Change from brand name (Propess) to generic name of IMP (dinoprostone). Revision of rationale, and statistical outcomes to reflect removal of time dependency within primary outcome. Pragmatic revision of safety reporting definitions for reportable SAEs and protocol-exempt SAEs not requiring expedited reporting (Section 8) Removal of SmPC and IB from appendices, being superseded by the implementation of a reference safety information document. Extension to 31st December 2020

CI and Sponsor Signature Page

Trial Name:	SOLVE
Protocol Version Number:	Version: 7.0
Protocol Version Date:	4th December 2019

This protocol has been approved by:

CI Name:	Prof Janesh Gupta	
Trial Role:	Chief Investigator	
Signature and date:		24 June 2020 __ __/ __ __/ __ __ __ __
Sponsor Name:	Miss Liz Adey	
On Behalf of:	Birmingham Women's and Children's NHS Foundation Trust	
Signature and date:		30 / 06 / 2020

PI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

This protocol has been approved by:

Trial Name:	SOLVE
Protocol Version Number:	Version: 7.0
Protocol Version Date:	04/12/2019

PI Name:	_____ _____
Name of Site:	_____
Signature and date:	_____ __ __ / __ __ / __ __ __ __

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RANDOMISATION

Telephone: 0800 2802 307 (24 hour automated service)

SAFETY REPORTING

Email SAE Forms to solve@trials.bham.ac.uk
or
Fax SAE Forms to: 0121 415 9136

TRIAL SUMMARY

Title
A randomised controlled trial of a synthetic osmotic cervical dilator for induction of labour in comparison to dinoprostone vaginal insert: the SOLVE trial

Trial Design
Phase III, Open, Multicentre, Superiority, Randomised Controlled Trial of a CE (*Conformité Européenne*/European Conformity) marked medical device and an Investigational Medicinal Product (IMP)

Primary Outcome Measures
Failure to achieve vaginal delivery

Participant Population
Women requiring cervical ripening for induction of labour (IoL)

Intervention
Experimental intervention: DILAPAN-S®
A synthetic osmotic cervical dilator for insertion into the cervical canal, using as many rods as necessary.

Control intervention: DINOPROSTONE
Slow release vaginal drug delivery system (Prostaglandin E_2).

Sample Size
860 women will need to be recruited.

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List of Abbreviations

AE	Adverse Event
AR	Adverse Reaction
BCTU	Birmingham Clinical Trials Unit
BWCNFT	Birmingham Women's and Children's NHS Foundation Trust
CE	Conformité Européenne/European Conformity
CI	Chief Investigator or Confidence Interval
CRF	Case Report Form
CTG	Cardiotocography
DMC	Data Monitoring Committee
DSUR	Developmental Safety Update Report
EC	European Commission
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
IB	Investigator Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IoL	Induction of Labour
ISF	Investigator Site File
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PG	Prostaglandin
PIS	Participant Information Sheet
PPH	Post-partum Haemorrhage
R&D	Research and Development
REC	Research Ethics Committee
RR	Relative Risk
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

1 Background and Rationale

1.1 Background

Induction of labour (IoL) is a commonly performed obstetric intervention. Over 25% of labours were induced in England during 2014-15 and the rate has been rising annually since 2008-09 (Health and Social Care Information Centre, 2015). IoL is generally carried out when the risks of continuing pregnancy outweigh the benefits. Maternal and fetal indications include post-term pregnancy, spontaneous rupture of membranes, pregnancy-induced hypertensive disorders, diabetes, thrombophilia, intrauterine fetal growth restriction, oligohydramnios, non-reassuring fetal status and fetal death (Hofmeyer et al., 2009; Mozurkewich, 2009; Boulvain 2001; Gülmezogulu, 2006; Irion, 1998).

In pregnancy, the uterine cervix retains its physical tubular structure by remaining firm during pregnancy as the uterus enlarges. In preparation for labour and delivery, the cervix undergoes a softening process and starts to dilate, a process called cervical ripening. These biochemical and physical changes are required for cervical dilation and successful labour and delivery of a fetus. There are various methods available to achieve cervical ripening (Hofmeyr et al., 2009). These include surgical methods (amniotomy alone or with oxytocin), pharmacological methods (prostaglandins in the form of vaginal gels, tablets or pessaries and oxytocin as a slow intravenous infusion) and mechanical methods (natural sea-weed laminaria tents, synthetic osmotic cervical dilator and balloon catheters introduced into or through the cervix and the extra-amniotic space).

Pharmacological methods in general promote cervical ripening through a direct effect on the cervical collagen matrix, which is transformed from a rigid tubular structure to a softer dilated structure. Local administration of prostaglandins, via a vaginal delivery system, is administered high into the posterior vaginal fornix and results in cervical ripening and simultaneously induces uterine contractions to complete labour (electronic Medicines Compendium, 2015). The release rate to the cervical tissue is continuous, which allows cervical ripening to progress. Ideally cervical ripening needs to occur before uterine contraction starts as this would mimic physiological process. Systemic side effects following the insertion of prostaglandins can occur and include nausea, vomiting, hypotension, tachycardia and uterine hyper-stimulation with additional effects on the fetus by causing fetal heart rate changes. Conversely, mechanical methods work by applying pressure to the internal and external cervical os and indirectly increasing local release of prostaglandin (PG) and oxytocin, or both. Osmotic dilators have an additional effect by dehydrating the cervix, which in turn softens the collagen matrix. Furthermore, mechanisms that involve neuroendocrine reflexes may promote the onset of uterine contractions (NICE, 2008). One of the main advantages of the mechanical methods is the absence of pharmacological related side effects.

In the United Kingdom (UK), the National Institute for Health and Care Excellence (NICE) recommends the use of vaginal hormone PG gels or pessaries (NICE, 2008). The Cochrane systematic review (Jozwiak et al., 2012) determined the effects of mechanical methods (i.e., laminaira tent, balloon catheter and extra-amniotic infusion) for cervical ripening or IoL in comparison with vaginal PGs and included 17 studies and 1,894 women. The proportion of women who did not achieve vaginal delivery within 24 hours was not significantly different (three studies; 586 women; RR 1.72; 95% CI 0.90 to 3.27) with no increase in caesarean sections (17 studies; 1,894 women; RR 1.07; 95% CI 0.91 to 1.25). There was a reduction in the risk of uterine hyper-stimulation and reduced risk of fetal heart rate changes when using mechanical methods (RR 0.16; 95% CI 0.06 to 0.39), reported in eight studies with a total of 1,203 participants.

In the meta-analysis conducted by Wang et al. (2016), a comparison of Foley catheter balloon to vaginal PGs included six studies with 1,453 women. There were no significant differences between the two ripening methods for vaginal delivery within 24 hours (five studies; 513 women; RR 0.75; 95% CI 0.43 to 1.30) or caesarean section (six studies; 400 women; RR 0.94; 95% CI 0.80 to 1.12). Vaginal PGs were related with increased rate of uterine hyper-stimulation compared to the mechanical methods (RR 0.07, 95% CI 0.03-0.19). The PROBAAT and PROBAAT-II studies found similar safety and effectiveness between Foley catheter compared with PG gel and misoprostol, respectively (Jozwiak et al., 2011; Ten Eikelder et al., 2016). The findings reported in the literature suggest that mechanical

methods seem to be as effective as vaginal PGs in achieving delivery within 24 hours, with fewer episodes of uterine hyper-stimulation. The risk of caesarean section did not differ and, therefore, mechanical methods can be considered to have fewer side effects compared with vaginal PGs. However, individual studies in the analyses had small sample sizes and used different comparators and protocols (NICE, 2014). Given that in the UK most National Health Service (NHS) Trusts administer vaginal PGs as recommended by NICE, this will be considered the standard (i.e., the comparator) intervention for the SOLVE trial.

A relatively under-researched method to induce labour is the deployment of synthetic osmotic cervical dilators. Initially utilised to prepare the cervix for a dilation and evacuation procedure for surgical termination of pregnancy, the dilator was researched 20 years ago as a method to ripen the cervix in preparation for labour (Roztocil et al., 1998; Chua et al., 1997; Gilson et al., 1996; Krammer et al., 1995). In addition to promoting the physiological release of endogenous PGs found within the cervix, the dilators dehydrate the cervix and make the osmotic dilation of the rod soften the cervix. Although the studies investigating the efficacy and safety of the dilators compared to a comparator (i.e., PG gel or no treatment) were relatively small and there were methodological limitations, the findings from these research papers found similar outcomes for labour. Furthermore, the synthetic osmotic cervical dilators had a significantly reduced risk of causing uterine hyper-stimulation (Chua et al., 1997) or painful contractions before cervical ripening occurs (Krammer et al., 1995). The decline in use of synthetic osmotic cervical dilators was not the result of safety or efficacy concerns, but rather from a general shift towards PGs.

There is now an urgent and pressing need to conduct large scale randomised controlled trials that compare mechanical procedures with pharmacological interventions in cervical ripening for IoL and report on both substantive and participant reported outcomes. The SOLVE trial will aim to conduct such a trial comparing a mechanical method (i.e., synthetic osmotic cervical dilator – Dilapan-S) with the standard pharmacological method (i.e., vaginal PG) used for IoL in the NHS.

1.2 Trial rationale

Given that current medical management should consider maternal comfort, suitability for outpatient management, requirement for fetal monitoring and provider control (Robinson et al., 2016), the use of synthetic osmotic cervical dilators to induce labour might provide an alternative choice for both clinicians and women. Furthermore, when NICE updated their guidelines in 2014 on the method of IoL, they recommended that there should be further research into the use of mechanical methods in situations where hormone methods carried risks. Subsequently, the Royal College of Obstetricians and Gynaecologist guidelines on vaginal birth after caesarean section has identified the direct association with uterine rupture to be attributed to vaginal PG use (RCOG, 2015), and called for further research on the use of mechanical methods in this group of women.

1.2.1 Justification for participant population

Any adult female who has a singleton pregnancy greater than 37 weeks and is deemed suitable for both mechanical and pharmacological IoL will be eligible for inclusion. The use of PGs in women who have had previous caesarean sections is considered off license for this drug, but for the SOLVE trial these women will be eligible for inclusion, as some maternity units in the UK do allow PG for IoL for intended vaginal delivery in women with one previous caesarean section. For the purposes of clarification, the inclusion and exclusion criteria stipulated in the SOLVE protocol will be followed.

1.2.2 Justification for design

Synthetic osmotic cervical dilators are similar in terms of efficacy and safety for delivering a fetus vaginally following IoL compared to pharmacological methods (Roztocil et al., 1998; Chua et al., 1997; Gilson et al., 1996; Krammer et al., 1995). However, these findings are based on clinical trials with relatively small sample sizes and limited methodological quality. It is, therefore, relevant to conduct a prospective phase III multi-centre randomised controlled trial of the synthetic dilators compared to the current standard PG treatment in the NHS as recommended by NICE. Although IoL is a commonly performed intervention, there are complexities that need to be considered during cervical ripening,

evaluation of successful vaginal delivery, parity and previous mode of delivery as important and necessary steps in the development of recommendations and guidelines for inducing labour. Given it will be difficult to successfully blind the clinician and the patient to intervention allocation, this trial will be conducted as an open label study. The primary outcome measure and the clinical decision to progress to a caesarean section are unlikely to be affected by knowledge of induction method allocation and, therefore, the risk of a bias in this open label design is considered to be minimal. However, it is important to acknowledge there might be a bias in such a design and, therefore, objective assessments such as neonatal wellbeing such as cord blood pH, lactate and Apgar scores have been included as outcome measures.

1.2.3 Choice of intervention

Synthetic osmotic cervical dilator (DILAPAN-S®)

DILAPAN-S® is a non-pharmacological synthetic rod, which is inserted into the cervical canal and through the internal os, for cervical ripening prior to induction. Its mode of action consists in the hydrophilic properties of the device absorbing fluids from surrounding tissue structures, thus expanding the volume of DILAPAN-S® rods, usually within a 12-hour period. Subsequently it exerts radial pressure on the surrounding structures (cervix) to dilate progressively. Endocervical pressure on the cervix results not only in its mechanical dilatation but the pressure on the endocervical structures also stimulates the production of endogenous PGs and promotes cervical ripening through its collagenolytic action. 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 sea-weed laminaria tents
- Certified production and non-porous synthetic material ensure higher safety in comparison to laminaria tents
- Easy application and storage in room temperature
- Sterile nature of the 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

Dinoprostone vaginal insert

Dinoprostone, as a slow release 10mg vaginal insert, is currently the standard method used for IoL in the NHS, particularly in nulliparous woman. The benefits for using DINOPROSTONE are:

- Larger proportion of women can go into spontaneous labour compared to mechanical methods (i.e., only 50% will require formal amniotomy and oxytocin administration)

- Simultaneous cervical ripening and initiation of uterine contractions
- Mimicking the physiological processes

However, there are risks associated with the use of DINOPROSTONE in the IoL. The most common include:

- Abnormal uterine contractions
- Requirement for fetal heart rate assessment by cardiotocography (CTG) monitoring for 20-30 minutes (dependent of local maternity unit protocol) before and after administration
- Uterine hyper-tonus / hyper-stimulation
- Premature uterine contractions before cervical ripening occurs causing pain during the cervical ripening period

1.2.4 Choice of outcome

A series of Cochrane reviews of methods of cervical ripening and labour induction used the primary outcome of vaginal delivery not achieved within 24 hours (Hofmeyr et al., 2009). The investigators of the PROBAAT-II study make the valid point that as an outcome of labour induction, giving birth vaginally is more important than how quickly it happens; therefore 24 hours may not be a long enough time for appropriate assessment. Indeed, the effect found in the PROBAAT-II study would have been reversed had the outcome been measured by assessing vaginal delivery with 36 hours. Therefore, we originally designed the SOLVE trial based on a primary outcome of failure to deliver vaginally within 36 hours. However, after the start of recruitment to the trial, the number of inductions substantially increased across the UK causing logistical delays in the induction process which impacted on the 36 hour window specified in the definition of the primary outcome. In June 2019 (after 290 women had been randomised) the Trial Steering Committee agreed to an amendment to the primary outcome removing the time limit. The removal of the time limit was also reiterated in a call to standardise the outcome measure in IoL trials to vaginal delivery without a time limit, particularly when mechanical methods are employed (Dos Santos et al., 2018). It is now recognised that in order to mimic the natural physiological process, cervical ripening should occur before uterine contractions start. It is instrumental that the cervical is soft and ripened before the uterus starts to contract. If the uterus contracts with an unfavourable cervix the process of IoL can be painful and potentially lengthened. This step wise induction process takes a longer time period and therefore the SOLVE trial defines the primary outcome measure as achieving a vaginal delivery.. The vaginal delivery rates within 24, 36 and 48 hours will be documented as secondary outcome measures for comparability with other studies.

2 Trial objectives

2.1 Primary objective:

To evaluate the effectiveness of the synthetic osmotic cervical dilator in cervical ripening, for IoL, in comparison to dinoprostone vaginal insert to achieve vaginal delivery.

2.2 Secondary objective:

To determine the response to a synthetic osmotic cervical dilator in cervical ripening, for IoL, in comparison to dinoprostone vaginal insert on maternal and neonatal outcomes.

3 Trial design and setting

3.1 Trial design

Phase III, Open, Multicentre, Superiority, Randomised Controlled Trial of a CE marked medical device and an Investigational Medicinal Product (IMP), which will aim to randomise 860 women.

3.2 Trial setting

Maternity units within the UK.

4 Eligibility

4.1 Inclusion criteria

Women must meet the following criteria prior to initiation of IoL:

1. ≥ 16 years of age
2. Able to provide informed consent
3. Singleton pregnancy
4. Indication for IoL
5. Pregnancy ≥ 37.0 weeks (assessed as an agreed gestational age by ultrasound dating scan)
6. Living fetus with vertex presentation
7. Intact membranes

4.2 Exclusion criteria

1. Women already receiving oxytocin
2. Diagnosis of fulminant preeclampsia / eclampsia
3. Contraindication to DINOPROSTONE or DILAPAN
4. If DINOPROSTONE for IoL is non-compliant with local policy
5. Enrolled in other randomised controlled trials of an IMP or device for cervical ripening or induction of labour

4.3 Co-enrolment

Women participating in SOLVE cannot join other interventional trials of an IMP or device for cervical ripening or induction of labour. They may be recruited to other intrapartum IMP studies. Women may be recruited to non-interventional trials such as observational or qualitative studies for induction of labour and to all other trials in pregnancy or the postnatal period.

Previous participation in SOLVE precludes participation by the same individual twice in the trial in a subsequent pregnancy.

5 Trial participant recruitment

A flowchart of the trial and participant recruitment process is shown in Appendix 1 and 2, respectively. Prior to women undergoing any trial-related procedures, informed consent will be obtained using an ethics approved Informed Consent Form (ICF). Research participants will not receive any payments, reimbursement of expenses, or any other benefits or incentives for taking part in this research.

5.1 Introduction to the trial

It is anticipated that a woman will be initially approached in clinic, when a decision to induce labour is made as part of the woman's standard care visit. Once the decision to induce labour is made they will be introduced to the trial and given a Participant Information Sheet (PIS) to read. At some hospitals, where women may be seen by a midwife in the community, the PIS may be handed out by the community midwife. The principal investigator or those delegated the responsibility at site will ensure that they adequately explain the aim of the trial, the trial interventions, the anticipated benefits and potential hazards of taking part in the trial to the women. They will also stress that participation is voluntary and that the woman is free to decline to take part and may withdraw from the trial at any time. The woman will be told that it may not be possible to remove or change the method of induction once started. She will be told that subsequent series may be required. Electronic copies of the PIS and ICF will be available from the Trials Office and will be printed or photocopied onto the headed paper of the local institution. At some centres all information is online and where that is the case, we will add the PIS to the centre's website.

5.2 Assessment of eligibility

Under the principles of GCP, the decision whether a patient is eligible for entry into a trial is considered to be a medical decision and therefore must be made by a medically qualified doctor. The obstetrician will check that the woman is eligible for the trial by completing and documenting eligibility in the patient's medical notes and on relevant case report forms.

When the woman attends her standard care visit to start the process of IoL, she will be (re-) approached by a GCP trained obstetrician or midwife delegated responsibility to ask if she is still interested in participating in the trial.

The principal investigator or those obstetricians delegated the responsibility at site and adequately trained in the principles of GCP will check eligibility. The obstetrician will need to review and sign the final checklist on the randomisation form. Details of all women approached during this visit about the trial will be recorded on the Screening Log, which will be maintained electronically. Fully anonymised copies of these logs will be returned to the trials office for review. Once eligibility is confirmed and the woman is still wishing to enter the trial, she will be asked to sign a consent form.

5.3 Consent

Full informed consent will be obtained after the eligibility criteria have been checked and just prior to randomisation. Consent will be obtained by a GCP trained obstetrician or midwife, delegated to do so on the delegation log. Prior to consent the women will be given the opportunity to ask questions she might have after reading the PIS. It will be reiterated to the women that participation is voluntary and that she is free to decline to take part and may withdraw from the trial at any time (although it may not be possible to remove or change the method of induction once started and this statement will form part of the informed consent form).

Details of the informed consent discussion will be recorded in the woman's medical notes. This will include date of discussion, the name of the trial, summary of discussion, the decision to accept or decline participation in the SOLVE trial, version number of the PIS given to the woman, version number of informed consent form signed by the participant and date consent was received.

Women who wish to enter the trial will be asked to initial, sign and date the latest version of the Informed Consent Form (ICF), which will have been approved by the research ethics committee. The Investigator (or a member of their team delegated the responsibility) will co-sign and date the form. A copy of the ICF will be given to the woman, a copy will be filed in the medical notes and the original placed in the ISF. A copy of the signed ICF will be transferred via email to the SOLVE trial office for review, and we are seeking explicit consent for this transfer of identifiable information in the ICF itself. Once the woman is entered into the trial, the participant's unique trial identification number will be entered on the ICF maintained in the ISF.

It is highly unlikely that any new external information that may be relevant to the woman's continued participation will arise, given the short duration of the intervention.

5.4 Randomisation

After all eligibility criteria have been confirmed and informed consent has been received, the women can be randomised into the SOLVE trial. This will be as close as possible to induction of labour commencing.

5.4.1 Minimisation

Women will be randomised in a 1:1 ratio to either:

1. synthetic osmotic cervical dilator
   or
2. 10-mg controlled-release dinoprostone vaginal insert.

Randomisation will be provided by a computer generated program hosted by the University of Aberdeen and checked by a statistician form Birmingham Clinical Trials Unit (BCTU), University of Birmingham using a minimisation algorithm to ensure balance between groups of the following variables:

- Randomising centre
- Nulliparous vs multiparous
- Maternal obesity: BMI >= 30 kg/m2 vs. BMI < 30 kg/m2 at the first antenatal consultation
- Maternal age: <20, 20 to <30, 30 to <40, 40+ years

A 'random element' will be included in the minimisation algorithm, so that each woman has a probability (unspecified here), of being randomised to the opposite intervention that they would have otherwise received. Full details of the algorithm used will be stored in a confidential document at the University of Aberdeen and BCTU. To avoid bias, the random allocation sequence is concealed from those responsible for recruiting participants into the study. Given the nature of the intervention, the SOLVE trial will not be a blinded trial.

5.4.2 Telephone randomisation procedure

The Principal Investigator, or delegated members of their team, can randomise a woman by a telephone call using a freephone number (**0800 2802 307**) to the Health Services Research Unit, University of Aberdeen who offer a 24-hour, seven day telephone randomisation service. It is anticipated that the task of randomising a woman will typically be delegated to a midwife, but it can be conducted by an obstetrician.

Randomisation Forms will be provided to investigators and should be completed and used to collate the necessary information prior to randomisation. Once all eligibility criteria have been provided, a Trial Number and intervention allocation will be given and relevant parties notified.

5.5 Informing the participants GP

Following the woman providing consent, her GP will be notified using the trial template 'Letter to GP', which will be sent from the participants' hospital on headed paper and a copy kept in the ISF.

5.6 Prescription

The provision of DINOPROSTONE or DILAPAN-S® will be under the supervision of senior clinician obstetrician (consultant or experienced Specialty Registrar), who will reconfirm that there are no contraindications to the administration of these interventions. For women under midwifery care where a patient group directive allows midwife prescription, the senior clinician can be the midwife (according to local policy). Local polices and processes will be used for all prescriptions.

5.7 Dispensing

The dispensing of either intervention is by an appropriate prescriber according to local arrangements. The allocated intervention should be administered by the obstetrician or midwife, in accordance with local policy.

5.8 Blinding

Given that it will be difficult to successfully blind the woman and clinical team to the intervention allocation, this trial will be conducted as an open label study.

6 Trial interventions

6.1 Interventions

The experimental intervention will be the synthetic osmotic cervical dilator (DILAPAN-S®) and the control will be control dinoprostone vaginal insert.

6.2 Intervention supply and storage

It is anticipated that both the DILAPAN-S® and DINOPROSTONE® will be stored at pharmacy or local to where IoL is conducted. A treatment log will be made available and completed by an appropriate person when an intervention is dispensed (see section 6.5 – Accountability procedures).

6.2.1 DILAPAN-S®

DILAPAN-S® is a class IIa medical device. The device is CE marked and available on the market for use wherever cervical softening and dilation are desired. Hydrogel rods are packed individually and distributed in boxes of 10 or 25 pieces. Medicem will provide the devices in their original sterilepackaging and with their original labelling. If any of the individual sterile packaging is found to be damaged or open the Dilapan pack should be rendered unsuitable for use. In that instance the study team should complete a Product Defect Form and return this to the Trials Office for review. The shelf life of DILAPAN-S® is 36 months. The device should be stored at room temperature.

6.2.2 DINOPROSTONE

The Medicines for Human Use (Clinical Trials) Regulations 2004 allows for particular situations where trial specific labelling is not required, namely where marketed products are being used within the terms of their marketing authorisation, being dispensed in accordance with a prescription given by an authorised health care professional and are labelled as per clinical standards. DINOPROSTONE is in routine use, is readily available from clinical hospital supplies and should be purchased via usual NHS Trust processes. DINOPROSTONE will therefore be used 'off-the-shelf' from normal labour ward supplies, stored as standard hospital stock, and no additional trial specific labelling or temperature monitoring will be required.

6.3 Dosing schedule

An overview of the dosing schedule for both DILAPAN-S® and DINOPROSTONE is given in Table 1, which include the maximum timeframes of when the Bishop score should be assessed.

Table 1: Overview of dosing schedule for DILAPAN-S® and DINOPROSTONE

DILAPAN-S®	BISHOP	INSERT (1st series)	REMOVE	INSERT (2nd series)
Baseline	x	x		
+12-24 hours	x		x	x
+24-48 hours	x		x	

PROPESS®	BISHOP	INSERT (1st series)	REMOVE	INSERT (2nd series)
Baseline	x	x		
+12 hours	x			
+24 hours	x		(x)	
+32 hours	x		x	x
+56 hours	x		(x)	
+64 hours	x		x	

Note: Local policies should be adhered to and times given above are intended for guidance only. This includes any timeframe given in local policies between the 1st and 2nd series for DINOPROSTONE as these may vary. The times should be considered as 'up to a maximum' from baseline (e.g., +24 hours, should be read as up to a maximum of 24 hours after baseline).

6.3.1 DILAPAN-S®

Prior to insertion of the rods, the cervix should be visualised with a sterile vaginal speculum and cleansed with an antiseptic. Up to a maximum of five rods per series can be inserted into the cervical canal, particularly making sure the tip of the Dilapan-S® rod crosses through the internal os. Each series of rod(s) should remain in place for a minimum of 12 hours (unless there is a reason for removal - see section 6.7.1) and up to a maximum of 24 hours. If the cervix remains unfavourable after the first series a second series of dilators can be used for an additional 12-24 hours. It is highly unusual to require more than two series of Dilapan-S® rods and may indicate that they have not been placed correctly through the internal os. Please review the training manual and video to correctly place the Dilapan-S® rods before attempting another series.

Synthetic osmotic dilators will be administered as per the manufacturer's instruction for use

It is recommended that a 20-30 minute CTG should be performed before each series of dilator insertion(s). NICE does not stipulate the need for any CTG monitoring after insertion, however local policy should be followed. This is not mandatory for trial inclusion.

The woman will be instructed to report any excessive bleeding, pain or other concerns. Under no circumstances should the woman try to remove the rod(s) herself.

6.3.2 DINOPROSTONE

DINOPROSTONE 10mg vaginal delivery system consists of a non-biodegradable polymeric drug eluting device delivering 10mg dinoprostone (Prostaglandin E_2) by slow release. This can be used in both nulliparous and multiparous women, including those with a previous lower segment caesarean section (according to local hospital policy). One DINOPROSTONE will be administered high up into the posterior vaginal fornix using only small amounts of water soluble lubricants to aid insertion. Each series of Dinoprostone should be used according to local policy, unless there is a reason for removal (see section 6.7.2).

The woman will be instructed to report any excessive bleeding, pain or other concerns. Under no circumstances should the woman try to remove the DINOPROSTONE herself.

6.4 Drug interaction and caution for use

6.4.1 DILAPAN-S®

There are no known drug interactions with DILAPAN-S®

6.4.2 DINOPROSTONE

The manufacturer recommends that nonsteroidal anti-inflammatory drugs, including aspirin, should be stopped before insertion of the dinoprostone delivery system. Caution should be used with dinoprostone intended for women with a history of asthma, epilepsy, glaucoma or raised intra-ocular pressure; with hypertension and with risk factors for disseminated intravascular coagulation or uterine rupture, including uterine scarring. Since dinoprostone may increase activity of oxytocic agents, concomitant use of dinoprostone and oxytocics is not recommended. At least 30 minutes should elapse between removal of dinoprostone vaginal insert and initiation of oxytocin therapy.

6.5 Accountability procedures

The trial is taking place on the induction/labour ward and both interventions will be dispensed, accounted for and reconciled as per local routine practice. A trial specific treatment log should be completed for each intervention and series used.

6.6 Discontinuation of intervention

The method of induction should be discontinued if they fulfil the criteria given below. Discontinuation or change of intervention is permitted within the trial if the healthcare providers consider it acceptable. Removal of the induction method does not constitute withdrawal from the SOLVE trial unless explicit withdrawal of consent is expressed, as detailed in Section 6.9.

Any clinical adverse event (AE) or deterioration of the maternal or fetal condition that occurs such that continued use of either induction method is no longer appropriate, should be managed as appropriate by the healthcare team. Any change or discontinuation in the initial induction approach should be recorded in the electronic case report form (eCRF) and medical notes and does not constitute withdrawal from the SOLVE trial.

6.6.1 Discontinuation of DILAPAN-S®

Reasons for removing dilators before onset of labour or earlier include:

1. Spontaneous onset of labour (defined as regular painful contractions)
2. Suspected fetal hypoxia
3. Where amniotomy is required
4. Serious systemic side effects like nausea, vomiting, hypotension, tachycardia
5. Spontaneous expulsion of dilators

6.6.2 Discontinuation of DINOPROSTONE

Reasons for discontinuation of the dinoprostone insert include:

1. Presence of regular moderate or strong uterine contractions occurring at a frequency of more than 5 contractions every 10 minutes, irrespective of any cervical change would be classified as uterine tachysystole. If there are additional fetal heart rate abnormalities this would be classified as uterine hyperstimulation
2. Uterine contractile abnormalities, non-reassuring fetal heart rate patterns or fetal hypoxia that requires clinical intervention
3. Spontaneous rupture of membranes or amniotomy
4. Serious systemic side effects like nausea, vomiting, hypotension or tachycardia
5. At least 30 minutes prior to starting an intravenous infusion of oxytocin

6.7 Failure to progress and subsequent management of labour

If labour is not instigated or progression is considered too slow, the healthcare team will determine the appropriate next steps for the woman, which may be amniotomy, oxytocin or caesarean section (see definitions below). The woman will remain in the trial until the she is discharged from hospital.

After expulsion or removal of synthetic osmotic dilators, or at least 30 minutes after completion of maximum recommended dosing period of the DINOPROSTONE, as per local policy), amniotomy and oxytocin is administered to those women who are not in labour. Bishop score will be calculated after removal of the ripening devices, by the attending physician or a member of the resident staff. Once Bishop score is assessed as favourable, subsequent management of IoL will be according to local hospital protocol.

6.7.1 Clinical definitions

The clinical procedures and definitions are referred to for the purposes of data collection and are consistent with NICE guidelines for intrapartum care for healthy women and babies (NICE, 2014).
General:

1. Fetal heart rate abnormalities during cervical ripening are documented if the CTG recording is evaluated as being abnormal by the local clinical team
2. Established labour is defined as there are regular painful contractions and there is progressive cervical dilatation from 4 cm
3. If delay in the established first stage is suspected, all aspects of progress in labour will be assessed when diagnosing delay, including:
    a. cervical dilatation of less than 2 cm in 4 hours for first labours,
    b. cervical dilatation of less than 2 cm in 4 hours or a slowing in the progress of labour for second or subsequent labours
    c. descent and rotation of the baby's head
    d. changes in the strength, duration and frequency of uterine contractions
4. Uterine tachysystole is identified when there are > 5 contractions in 10 minutes for at least 20 minutes
5. Uterine hypertonus is defined as a single contraction lasting at least 2 minutes
6. Uterine hyperstimulation is defined as tachysystole with fetal heart rate abnormalities
7. Failed induction is diagnosed when women do not progress into the active phase of labour despite adequate contraction patterns, after amniotomy and a minimum of 10 hours of oxytocin infusion

8. After starting oxytocin in established labour, a vaginal examination is required 4 hours later and if cervical dilatation has increased by less than 2 cm after 4 hours of oxytocin, further obstetric review is required to assess the need for caesarean section

6.8 Withdrawal and re-confirmation of consent

Whilst the study is undertaken on the ward, within a limited time period, participants should be asked about their ongoing willingness to continue participation. This will be checked in accordance with the principles of GCP throughout the trial and should be documented in the participant medical records. CRFs/participant questionnaires will also be used to document a participant's willingness to continue in the trial.

Participants may withdraw their consent at any time during the trial. They may do this without giving a reason. There are different types of withdrawal and a list of potential examples (but not exhaustive), are detailed below:

1. Woman would like to withdraw from the intervention but has agreed to provide follow-up data, both routine and trial specific, for use in the trial analysis
2. Woman would like to withdraw from the intervention but is willing to be followed up as part of standard clinical care (e.g., the woman has agreed that follow-up data collected as standard can be used in the trial analysis)
3. Woman is not willing to be followed up for trial purposes (e.g., the woman has agreed that any data collected prior to the withdrawal of consent can be used in the trial analysis)
4. Woman wishes to withdraw and that none of their data collected to date be used for any trial purposes

The following details of withdrawal should be clearly documented on the eCRF, a trial withdrawal form or equivalent and where applicable in the medical notes:

1. The date the woman withdrew consent
2. The reason, if given
3. Type of withdrawal, from the definitions above

Once the process of inducing cervical ripening has commenced, a maternal request to change methods or suspend the induction process may not be clinically possible. If a woman withdraws consent for continued participation, consent should be sought to collect method of delivery as a minimum and ideally all subsequent data. If a woman withdraws consent for subsequent data collection, all data collected to that point will be retained unless she explicitly requests redaction of all her data. If she loses capacity during the trial, data until the point of loss of capacity will be retained.

7 Trial assessments and outcomes

Table 2: ***Trial participant schedule of events and summary of assessments***

		Pre-enrolment	Enrolment	Allocation	Intervention			Outcome	
	TIMEPOINT	***Induction clinic visit***	***At admission***	***Prior to induction***	***Day 1***	***Day 2***	***Day 3***	***Delivery***	***Discharge***
ENROLMENT	**PIS provided**	X	X						
	Eligibility screen	X	X	X					
	Informed consent		X						
	Randomisation			X					
INTERVENTION	**DILAPAN-S**				X	X			
	DINOPROSTONE				X	X	X		
	Intervention end				X	X	X		
ASSESSMENTS	**Baseline data collection**			X					
	Maternal and neonatal outcome data collection							X	X
	SAEs/SUSARs				X	X	X	X	X
	Maternal satisfaction								X

7.1 Outcome measures

7.1.1 Clinical outcome measures

Primary outcome: Failure to achieve vaginal delivery.

7.1.2 Secondary outcomes

Maternal outcomes

During cervical ripening

- Change in Bishop score from baseline to completion of cervical ripening
- Time between Bishops scores measured at baseline and completion of cervical ripening
- Use of analgesia during cervical ripening (including insertion of intervention)
- Time between randomisation and start of analgesia use for cervical ripening
- Any complications during cervical ripening

During labour and immediately after delivery

- Time between removal of last series of intervention to amniotomy
- Time between first insertion of intervention to when labour started
- Amniotomy undertaken for induction of labour
- Amniotomy undertaken for augmentation of labour

- Required oxytocin for induction of labour
- Required oxytocin for augmentation of labour
- Use of analgesia / anaesthesia (e.g. epidural) during labour
- Any complications during or after labour
- Failure to achieve vaginal delivery within 24 hours from randomisation
- Failure to achieve vaginal delivery within 36 hours from randomisation
- Failure to achieve vaginal delivery within 48 hours from randomisation
- Spontaneous vaginal delivery
- Instrumental delivery due to delay in 2nd stage of labour and/or fetal heart rate abnormalities and/or abnormal FBS
- Caesarean section delivery due to delay in 1st and/or 2nd stage of labour, and/or fetal heart rate abnormalities and/or abnormal FBS

<u>After delivery until discharge</u>
- Complications from delivery until discharge (e.g., PPH, vaginal and uterine infections)
- Antibiotic use for pelvic infection (vaginal infection and/or endometritis)
- Duration of antibiotic use for pelvic infection
- Length of stay from randomisation

<u>Maternal satisfaction</u>
- Maternal satisfaction during insertion of intervention, cervical ripening, and overall (using a questionnaire consisting of 23 questions; responses to each question will be described)

<u>Neonatal outcomes</u>
- Baby born alive
- Birthweight
- APGAR score at 1 minute
- APGAR score at 5 minutes
- APGAR score at 10 minutes
- Meconium staining noted
- Metabolic acidosis (defined as cord-artery pH < 7.05 with base deficit ≥ 12mmol/l; lactate measures will be used instead of pH, where possible)
- Requirement of review by doctor from neonatal team (excluding routine checks)
- Antibiotic use for neonatal infection
- Duration of antibiotic use for neonatal infection
- Admitted to neonatal unit
- Length of stay in neonatal unit

<u>Process outcomes</u>
- Total duration of intervention received (regardless of any change of intervention)

<u>For each series (1 to 3):</u>
- Intervention received
- Reason allocated intervention not received
- Number of rods inserted if Dilapan received
- Duration of intervention received
- Number of occurrences when intervention received falls out
- Number of occurrences when intervention received is re-inserted
- Number of occurrences when the intervention received is removed due to complications
- Inability to fit the allocated intervention
- Additional series required and reasons

7.2 Screening

Details of all women approached after a decision to induce labour is made by an obstetrician or midwife will be recorded on the Screening Log (mothers name, mothers age, ethnicity, reason for non-inclusion and date of screening), which will be maintained within the ISF. Fully anonymised copies of these logs will be returned to the trials office for review.

7.3 Trial duration

Women will participate during induction of their labour and birth of her baby (usually 1-3 days) and followed up until they are discharged from their initial hospitalisation (the only exception to data being collected exclusively whilst the woman and her baby is in hospital, would be an ongoing SAE post-discharge, which will be collected up to resolution of the event).

7.4 Trial procedures

Dosing regimens should be followed as described in Section 6.3 (Dosing Schedule).

8 Adverse event reporting

8.1 General definitions

Adverse Event	AE	Any untoward medical occurrence in a participant or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Comment: An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of a (investigational) medicinal product, whether or not related to the (investigational) medicinal product.
Adverse Reaction	AR	All untoward and unintended responses to an IMP related to any dose administered. Comment: An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.
Serious Adverse Event	SAE	Any untoward medical occurrence or effect that: • Results in death is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Is a congenital anomaly/birth defect • Or is otherwise considered medically significant by the Investigator** Comments: *Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Serious Adverse Reaction	SAR	An Adverse Reaction which also meets the definition of a Serious Adverse Event
Unexpected Adverse Reaction	UAR	An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product). When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
Suspected Unexpected Serious Adverse Reaction	SUSAR	A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR. Comments: Medical judgment should be exercised in deciding whether an SAE or SAR should be reported expediently to the competent authorities (the Medicines and Healthcare products Competent Agency (MHRA) in the UK) and ethics committee in other situations. Examples include: • An increase in the rate of occurrence or a qualitative change of an expected SAR, which is judged to be clinically important • Post-study SUSARs that occur after the patient has completed a clinical trial and are reported by the Investigator to the Sponsor A SAR which is related to a non-IMP and which does not result from a possible interaction with an IMP is not a SUSAR.

8.2 Reporting requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. The Investigator will assess the seriousness and causality (relatedness) of all AEs experienced by the participant. This should be documented in the source data with reference to the SOLVE Reference Safety Information (RSI) document, which contains the pertinent details from the SmPC for Dinoprostone vaginal insert and Investigator Brochure for Dilapan-S.

The SOLVE Trial team will review the RSI on an annual basis and provide sites with updates as necessary.

8.3 Adverse Event (AE) reporting in SOLVE

AEs are commonly encountered in participants receiving Dinoprostone vaginal insert and Dilapan-S. As the safety profiles for both interventions used in this trial are well characterised, only the following events will be reported during treatment:

Maternal complications:

- Clinical diagnosis consistent with:
  - Vaginal infection
  - Endometritis
  - Uterine infection
- Secondary post-partum haemorrhage (>500ml)

Neonatal complications:

- Neonatal sepsis
- Meconium aspiration

The following are not AEs and do not require reporting:

1. A pre-existing condition (unless it worsens significantly during treatment)
2. Diagnostic and therapeutic procedures, such as caesarean section
3. Consequences of diagnostic and therapeutic procedures unrelated to the use of DINOPROSTONE/Dilapan-S (i.e. Urinary Tract Infection – UTI)

8.4 Serious Adverse Event (SAE) reporting in SOLVE

A Serious Adverse Event (SAE) is any Adverse Event (AE), that:

- results in death
- is life-threatening*
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity**

*Life-threatening in the definition of a SAE refers to an event in which the mother was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. Important adverse events that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the pregnancy or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

**The definition of a SAR or SAE usually includes any congenital anomaly or birth defect in any pregnancy; however, the intervention is given briefly towards the end of labour beyond 37 weeks' gestation where it cannot have any possible teratogenic effect. Any babies with congenital anomalies will not be considered to be a SAR or SAE.

8.4.1 Events that require expedited (immediate) reporting

Principal Investigators will report all SAEs that are defined in the protocol as an event which requires expedited reporting and occur from the commencement of the trial treatment until discharge. They must be recorded on the SAE form, and recorded in the medical notes and CRF.

The following events **require expedited reporting in SOLVE:**

Maternal outcomes

- uterine rupture / hysterectomy
- maternal sepsis*
- maternal admission to HDU / ITU - requiring critical care level 2 or 3
- maternal death
- maternal stay > 3 days following vaginal delivery (including instrumental delivery) and > 5 days after caesarean section
- Uterine dehiscence observed during caesarean section

***Maternal Sepsis**

In order to be considered an SAE we would expect maternal infection to be severe to justify expedited reporting. For example, as a guide, this is likely to be a clinical diagnosis of severe sepsis (with two or more of the following described in the symptoms of maternal sepsis table below):

Symptoms of maternal sepsis	
a	Temperature >38°C or<36°C measured on two occasions at least four hours apart
b	Heart rate >100 beats/minute measured on two occasions at least four hours apart
c	Respiratory rate>20/minute measured on two occasions at least four hours apart
d	White cell count >17x109/L or 10% immature band forms, measured on two separate occasions

Neonatal outcomes

- unexpected provision of neonatal **intensive** care ≥ 12 hours
- Neonatal sepsis
  - A neonate that requires antibiotics for more than 5 days
- neonatal seizures
- neonatal encephalopathy
- the need for neonatal therapeutic hypothermia
- Intrapartum stillbirth
- neonatal death

- Any other event deemed serious by the local PI, which does not meet the requirement of section 8.3.2.

Relatedness and severity of the SAE will be assessed by the Principal Investigator (or medically qualified delegate). The following categories will be used to define the relatedness (causality) of the SAE:

Table 3: **Categorisation of causality for all events**

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out	**Related**
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 or medication)	
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 events or medication)	**Unrelated**
Not related	**There is no evidence of any causal relationship**	

On becoming aware that a participant has experienced an SAE, the Principal Investigator or delegate(s) should report SAE to their own Trust in accordance with local practice and to the SOLVE trials office.

To report as SAE to the SOLVE office, the Investigator or delegate(s) must complete, date and sign the trial specific BCTU SAE form. The completed form should be emailed or faxed to the SOLVE trials team using the details listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE:
Email the SAE Form to: **solve@trials.bham.ac.uk**
Or Fax to: 0121 415 9136

On receipt of an SAE form, the SOLVE trials team will allocate each SAE a unique reference number and return this via email to the site as proof of receipt. If the site has not received confirmation of receipt of the SAE from the SOLVE or if the SAE has not been assigned a unique SAE identification number, the site should contact the SOLVE trials team within 1 working day. The site and the SOLVE trials team should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the ISF.

Where an SAE Form has been completed by someone other than the Principal Investigator, the original SAE form will be required to be countersigned by the Principal Investigator to confirm agreement with the causality and severity assessments.

Following reporting of an SAE for a participant, the participants should be followed up until resolution or stabilisation of the event. Follow-up information should ideally be provided on a new SAE Form using the SAE reference number provided by the SOLVE trials team. Once the SAE has been resolved, all follow-up information has been received and the paperwork is complete, the original SAE form that was completed at site must be returned to the SOLVE trial office and a copy kept in the ISF

On receipt of an emailed SAE form from the site, the SOLVE trials team will allocate each SAE form with a unique reference number and enter this onto the SAE form in the section for office use only. The SAE form (containing the completed unique reference number) will be forwarded to the site as proof of receipt within 1 working day. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE and filed with the actual SAE in the TMF.

On receipt of an SAE Form the CI or delegate will independently determine the seriousness and causality of the SAE. An SAE judged by the CI or delegate(s) to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The causality assessment given by the PI will not be downgraded by the CI or delegate(s). If the CI or delegate(s) disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

The CI or delegate(s) will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the Reference Safety Information (RSI) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

8.4.2 Events that do not require expedited (immediate) reporting

The following SAEs do not require expedited reporting as a consequence of the nature of the patient population enrolled in SOLVE. These events are pre-specified outcomes and are all captured on the CRFs. They do NOT require completion of a SAE form and they do NOT require reporting to the SOLVE trial office:

Maternal events

- A pre-existing maternal condition (such as renal disease), unless it causes increased clinical concern
- Retained placenta
- Postpartum haemorrhage
- Prolonged stay for psychiatric or social reasons;
- Prolonged hospital stay of the mother due to the need to keep her baby in hospital;

Neonatal events

- Admission to Neonatal Unit for pre-existing condition
- Prolonged stay for baby due to maternal condition

8.5 Device deficiencies relating the Dilapan-S

Device deficiencies (not meeting the requirement of an SAE) related to DILAPAN-S® need to be reported by the principal investigator (or delegate) to the SOLVE trial office using the product defect form. The SOLVE trial team will then report to the device manufacturer (See section 8.7).

Reporting to the Competent Authority and main Research Ethics Committee

8.6 Suspected Unexpected Serious Adverse Reactions

The SOLVE trials office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA), main REC and Sponsor within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as non-life threatening SUSARs will be reported within 15 days.

8.7 Serious Adverse Reactions

The SOLVE trials office will report details of all SARs (including SUSARs) to the MHRA main REC and Sponsor annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR).

8.8 Other safety issues identified during the course of the trial

The MHRA and REC will be notified immediately if a significant safety issue is identified during the course of the trial. The sponsor will also be informed at the time that the REC and MHRA is informed.

8.9 Reporting to investigators

Details of all SUSARs and any other urgent safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

8.10 Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs.

8.11 Reporting to third parties (Medicem)

Medicem Technology S.R.O is the manufacturer of Dilapan-S and is providing funding for the trial and supplying the device. As such, they will be notified of safety information relating to DILAPAN-S® resulting from the trial. The SOLVE trial office will notify Medicem of AEs and SAEs, and device deficiencies relating to DILAPAN-S®. using Medicem's Incident Compliant Form. Information on this form will be transposed by BCTU from the respective product defect form received from sites and will omit any participant identifiable data.

In relation to DILAPAN-S®, the SOLVE Trial is a Post-Market Clinical Follow-up study conducted using a CE-marked medical device within its intended use. The provisions of Article 59 of the Regulation (European Commission; EC) No 2012/0266 (device deficiency, adverse events and SAEs reporting) and any legal provisions related to non-CE marked medical devices or CE-marked devices used outside their intended use, do not apply.

The provisions of the Regulation (EC) No 2012/0266 concerning information and notification of any malfunction or deterioration in the characteristics or performance of the DILAPAN-S® made available on the market, any inadequacy in the labelling or information supplied by Medicem Technology and any unexpected undesirable side-effect, or any incident that directly or indirectly led, might have led or might lead to death of a patient, user or other person, temporary or permanent serious deterioration of the patient's, user's or other person's state of health, or serious public health threat occurring following placing devices on the market are fully applicable.

9 Data handling and record keeping

9.1 Source data

The source date for all data other than the maternal satisfaction questionnaire will be the women's medical notes and the neonatal notes. The paper maternal satisfaction questionnaire is source data,

being a participant reported outcome. Paper copies of the eCRF are provided to sites. The paper forms are not considered to be part of the CRF and are merely provided as tools to facilitate accurate collection and will be considered as part of source data where applicable.

9.2 Electronic Case Report Form (eCRF) completion

Data reported on each form will be consistent with the source data and any discrepancies will be explained. Staff delegated to complete forms will be trained to adhere to:

- Date format and partial dates
- Time format and unknown times
- Rounding conventions
- Trial-specific interpretation of data fields
- Entry requirements for concomitant medications (generic or brand names)
- Which forms to complete and when
- What to do in certain scenarios, for example when a woman withdraws from the trial
- Missing/incomplete data
- Completing SAE forms and reporting SAEs
- Protocol and GCP non-compliances

In all cases it remains the responsibility of the site's Principal Investigator to ensure that the eCRFs have been completed correctly and that the data are accurate. Each form should be signed by the site's Principal Investigator or delegate, for example a research midwife.

The site will be required to enter the data directly on to the eCRF within the trial database at site.

9.3 Data management

Case Report Forms can be entered online at https://www.trials.bham.ac.uk/SOLVE. Authorised staff at sites (and at the trials office) will require an individual secure login username and password to access this online data entry system. Those entering data will receive written work instructions on the process (a copy of which should be filed in the ISF and TMF)..

If changes need to be made to an eCRF that has already been entered and submitted on to the database, the site should contact the SOLVE trial office so that the form can be checked out to them and an explanation of the errors entered. If it is not obvious why a change has been made, an explanation should be written next to the change within the database.

Data reported on each CRF should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the eCRF. Completed questionnaires will be analysed by the study coordinators for completeness. All missing and ambiguous data will be queried. The online data base system can be used to generate any missing data queries. These will be generated on a regular basis by trial office staff and reported to the site for clarification as soon as is possible. The process of entering data on to the database, itself forms a data quality check, as ranges are put in place to ensure that only viable data values can be input. It will be the responsibility of the Principal Investigator to ensure the accuracy of all data entered in the eCRFs. The SOLVE trial Delegation Log will identify all those personnel with responsibilities for data collection

eCRFs may be amended and the versions updated by the SOLVE trial office, as appropriate, throughout the duration of the trial. Whilst this may not constitute a protocol amendment, new versions of the eCRFs must be implemented by participating sites immediately on receipt.

9.4 Archiving

Archiving will be authorised by the SOLVE trial office on behalf of the Sponsor following submission of the end of trial report.

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source documents (e.g. signed Informed Consent Forms, ISFs, Pharmacy Files, womens' hospital notes, copies of CRFs etc.) at their site are securely retained as per their NHS Trust policy, for at least 25 years after completion of the trial.

Destruction of essential documents will require authorisation from the SOLVE trial office on behalf of the Sponsor.

10 Quality control and quality assurance

10.1 Site set-up and initiation

10.1.1 Initial set-up

Each Centre should nominate an obstetrician to act as the local Principal Investigator and bear responsibility for the conduct of research at their centre. Close collaboration between all clinical teams is particularly important in SOLVE. All participating Principal Investigators will be asked to sign the necessary agreements and supply a current CV to the SOLVE trials office. Prior to commencing recruitment all sites will undergo a process of initiation, specific trial training and will have completed GCP training. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial. The SOLVE trials office must be informed immediately of any change in the site research team.

The local Principal Investigator is responsible for the overall conduct of the trial at the site and to ensure compliance with the protocol and any amendments. In accordance with the principles of GCP) the following areas listed in this section are also the responsibility of each Investigator. Responsibilities may be delegated to an appropriate member of trial site staff. Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable trial-related procedures. The listed responsibilities are:

- Ensure they are aware of the Data Protection Act, The Caldicott Principles and relevant Trust information policies
- Consent must be sought before using the information for any other purpose
- Ensure they are aware of the Health and Safety act and Trust policy - including the implications for themselves and participants
- Report adverse events or suspected misconduct to the REC and R&D Office
- Keep the original signed consent form and information sheet secure
- Ensure completion and appropriate storage of all study related data collection forms
- Seek consent prior to recruitment if the patient is under the care of another health care professional
- Ensure that only researchers with a contractual relationship with the Trust hosting the research make contact with patients. There are procedures in place for issuing honorary contracts
- Consider client diversity and be responsive to their information needs
- Keep women up-to-date on the progress of the research and provide feedback at the end of the study
-
- Monitor REC approval dates to check approval is still valid
- Provide annual progress reports to R&D office
- Disseminate research findings to R&D Committee after completion (contractual obligations permitting) but prior to publication
- Able to arrange for secure storage of the trial related documents for 25 years

10.1.2 Early follow-up

In addition the SOLVE trial office team will aim to perform an early follow-up study visit/teleconference, after data has been entered for the first two participants from that centre.

10.2 Monitoring

Monitoring of this trial will be to insure compliance with the principles of Good Clinical Practice (GCP)

10.2.1 On-site monitoring

Monitoring will be carried out, as required, following a risk assessment and as documented in the monitoring plan. Any monitoring activities will be reported to the trials team and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of participant withdrawals or deviations. These visits will be undertaken by a qualified monitor employed by the sponsor. The threshold for a triggered on-site monitoring visit will be detailed in the monitoring plan. If a monitoring visit is required the sponsor will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the sponsor representative access to source documents as requested.

10.2.2 Central monitoring

The SOLVE trials office will be in regular contact with the site research team to check on progress and address any queries that they may have. The SOLVE trials office will check incoming CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be asked for missing data or clarification of inconsistencies or discrepancies. Sites will be requested to send in copies of signed Informed Consent Forms and other documentation for in-house review for all participants providing explicit consent.

10.3 Audit and inspection

The Principal Investigator will permit trial-related monitoring, quality checks, audits, ethical reviews, and regulatory inspection(s) at their site, providing direct access to source data/documents. The Principal Investigator will comply with these visits and any required follow up. Sites are also requested to notify the SOLVE trials office of any MHRA inspections.

10.4 Close of trial

The trial team will arrange for a site visit/teleconference at the point of close of trial, to go through the procedure for ending the SOLVE trial.

10.5 Notification of serious breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial, within 7 days of becoming aware of that breach.

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree the safety or physical or mental integrity of the subjects of the trial; or the scientific value of the trial. Sites are therefore requested to notify the SOLVE trials office of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the SOLVE trials office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the SOLVE trials office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action. Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any

major problems identified during monitoring may be reported to the TMG, TSC and DMC, the REC and the relevant regulatory bodies such as the MHRA. This includes reporting serious breaches of GCP and/or the trial protocol to the REC and MHRA. A copy is sent to the sponsor at the time of reporting to the REC, MHRA and/or relevant regulatory bodies.

End of trial definition

The end of trial will be 90 days after the last woman has been discharged from their hospitalisation for IoL (the only exception to data being collected exclusively whilst the woman or her baby are in hospital, would be an ongoing SAE, which will be collected up to resolution of the event). This will allow sufficient time for the completion of protocol procedures, data collection, input and analyses. The SOLVE trials office will notify the MHRA and REC that the trial has ended within 90 days of the end of trial. Where the trial has terminated early (as defined in the clinical trial agreement or based on the DMC decision/recommendation), the SOLVE trials office will inform the MHRA and REC within 15 days of the end of trial. The SOLVE trials office will provide them with a summary of the clinical trial report within 12 months of the end of trial. A copy of the end of trial notification, as well as the summary report, is also sent to the sponsor at the time of sending these to the MHRA and REC.

11 Statistical considerations

11.1 Definition of outcome measures

Refer to section 7.2.1 Clinical Outcome Measures. The primary outcome is the failure to achieve vaginal delivery, regardless of whether it was unassisted or instrumental and regardless of whether it was a live or still birth.

11.2 Analysis of outcome measures

A separate Statistical Analysis Plan will provide a detailed description of the planned analyses. A brief outline is given as:

- Point estimates, 95% confidence intervals and p-values from two-sided tests will be calculated for all outcome measures. Outcomes will be adjusted for the minimisation variables where possible (section 5.6 Randomisation). Analysis will be of all randomised women in the intention to treat population.
- For all binomial outcomes, log-binomial regression models will be used to calculate relative risks and 95% confidence intervals. The p-value from the associated chi-squared test will be produced and used to determine statistical significance.
- Time from randomisation to delivery will be analysed by log-rank test with a Cox proportional hazard model also built if the assumptions of proportionality are met.
- Standard methods will be used to analyse other outcomes. Appropriate summary statistics split by group will be presented for each outcome (e.g., proportions/percentages, mean/standard deviation or median/interquartile range).

11.3 Planned subgroup analyses

Subgroup analyses will be limited to the variables listed in section 5.6.1 Minimisation (not including centre). Tests for statistical heterogeneity will be performed prior to any examination of effect estimates with subgroups. The results of subgroup analyses will be treated with caution and used for the purposes of hypothesis generation only.

11.4 Planned interim analyses

Interim analyses will be conducted on behalf of the DMC. These will be considered together with a full safety report including SAEs. The DMC will meet before recruitment commences, and thereafter at least annually. Effectiveness and futility criteria will be ratified by the DMC; suggested stopping criteria are based on a pragmatic approach with further details given in section 13.5 Data Monitoring Committee. The DAMOCLES charter will be adopted by the DMC and will include a specific remit for reviewing emerging data from other trials.

11.5 Planned final analyses

The primary analysis for the study will occur after all randomised women have completed full follow-up and outcome data has been entered into the study database.

11.6 Power calculations

The original sample size calculations were based on a primary outcome of failure to deliver vaginally within 36 hours as detailed here :

The justification for the sample size is based on estimates from previous studies (Edwards et al., 2014; Cromi et al., 2012; Jozwiak et al., 2011) of the vaginal birth rate within 36 hours in the DINOPROSTONE group. In these studies the rate of failure to deliver vaginally within 36 hours varies between 30% and 40% with DINOPROSTONE. Examples of sample sizes are given in **Table 7** and each detecting a plausible effect size of an absolute reduction of 8-9% has been selected as the difference to detect with 80% power (alpha=0.05):

Table 7: Overview of power calculations for the SOLVE trial

Absolute reduction of 9%*	No. of participants per group	No of participant total
40% - >31%	443 participants	886 participants
35% - >26%	**410 participants**	**820 participants**
30% - >21%	367 participants	734 participants

*Absolute reduction of 9% in failure to deliver vaginally with 36 hours

Note: figures highlighted in bold indicate the sample size for this trial.

To detect an absolute difference of 9% between groups in the primary outcome using the standard method of difference between proportions and assuming a 35% failure to deliver vaginally in the DINOPROSTONE group (i.e. 35% down to 26%) with 80% power and a type I error rate of 5%, a total of 410 participants per group will need to be randomised, 820 in total. Assuming and adjusting for approximately 5% loss to cross-over rate, 860 participants will need to be recruited. If the rate in the DINOPROSTONE group is as high as 40% or as low as 30% we will have between 77% and 84% power to detect an absolute difference of 9%.

The TSC agreed to the change in definition of the primary outcome to failure to achieve vaginal delivery in June 2019 (see section 1.2.4 for justification). The interim pooled estimate (combining both the DINOPROSTONE and DILAPAN groups) of the rate for the revised primary outcome based on recruitment up to 28th May 2019 was 36.6% (106/290) (95% CI 31.1% to 42.4%). Using this to provide a range of estimates of the control group rate, and assuming 80% power and a 5% two-sided significance level, the treatment effects that could be detected with a sample size fixed at 860 (the original sample size) are given in Table 8.

Table 8: Treatment effects for a fixed sample size and various control group rates

Assumed DINOPROSTONE group rate	Derived DILAPAN group rate	Absolute risk reduction
25%	17.2%	7.8%
30%	21.6%	8.4%
35%	26.2%	8.8%
40%	30.8%	9.2%
45%	35.6%	9.4%
50%	40.5%	9.5%

Since the primary analysis is based on an intention-to-treat population, adjusting for cross-over is not necessary. Therefore a total sample size of 860 women (430 per arm) would be sufficient to detect a plausible and clinically meaningful effect size of an absolute reduction of 8-9%, as originally planned.

11.7 Missing data and sensitivity analyses

Every attempt will be made to collect full follow-up data on all women (unless a woman withdraws consent for follow-up data collection). In particular, women will continue to be followed-up even after any protocol treatment deviation or violation. It is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis. This presents a risk of bias, and secondary sensitivity analyses will be undertaken to assess the possible impact of the risk. This may include simulating missing responses using a multiple imputation approach.

12 Trial organisational structure

12.1 Funder

Medicem Technology S.R.O CR is the manufacturer of DILAPAN-S® and is funding the SOLVE trial and providing the DILAPAN-S® device for the purpose of the trial.

12.2 Sponsor

Birmingham Women's and Children's NHS Foundation Trust (BWCNFT) will act as sponsor for the SOLVE Trial, taking overall responsibility for the initiation and management of the trial, and oversight of financing.

12.3 Trials office

The SOLVE trial office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for providing all trial materials, including the trial folders containing printed materials and the update slides. These will be supplied to each collaborating centre, after relevant R&D approval has been obtained. Additional supplies of any printed material can be obtained on request. The SOLVE trial office will provide the central randomisation service (via Aberdeen) and is responsible for collection and checking of data (including reports of SAEs thought to be due to trial interventions), for reporting of serious and unexpected adverse events to the sponsor and/or regulatory authorities and for analyses. The SOLVE trial office will help resolve any local problems that may be encountered in trial participation.

12.4 Trial management group

The Trial Management Group (TMG) will comprise the CI, statistician and other lead investigators (clinical and non-clinical) and members of the BCTU. The TMG will be responsible for the day-to-day running and management of the SOLVE trial. The TMG and sponsor representative will convene at regular intervals.

12.5 Trial steering committee

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial. The TSC will monitor trial progress and conduct and advice on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC. Further details of the remit and role of the TSC are available in the TSC Charter.

12.6 Data monitoring committee

Data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further women. The DMC will operate in accordance with a trial specific charter based upon the template created by the DAMOCLES charter. The DMC will meet at least every 12 months unless there is a specific reason (e.g. safety phase) to amend the schedule.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the TSC and TMG who will convey the findings of the DMC to the MHRA, ethics committee, funders and sponsor as applicable.

The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable, or if any issues are identified which may compromise participant safety following review of all SAEs. The trial would also stop early if the interim analyses showed differences between interventions that were deemed to be convincing to the clinical community. The trial stopping rules will be outlined in the DMC charter.

13 Finance

This is an investigator-initiated and investigator-led trial funded by Medicem, the manufacturers of DILAPAN-S®, in the form of an unrestricted educational grant. The grant will be administered by the sponsor (Birmingham Women's and Children's Hospital).

14 Ethical considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the General Data Protection Regulation and Data Protection Act 2018, EU Clinical Trials Directive, Medical Devices Regulations and amendment Regulations, and Guidelines for Good Clinical Practice (GCP). This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the REC prior to circulation.

Before any women are enrolled into the trial, the Principal Investigator at each site is required to obtain local R&D approval. Sites will not be permitted to enrol participants until written confirmation of R&D approval is received by the Principal Investigator.

It is the responsibility of the Principal Investigator to ensure that the trial will be conducted in compliance with the protocol at their site, and that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual women.

15 Confidentiality and data protection

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation and Data Protection Act 2018.

Participants will always be identified using only their unique trial identification code on the Case Report Form and during correspondence between the SOLVE trials office and the participating site. The women will be informed about the transfer of the non-identifiable data and information to the SOLVE trial office at the BCTU and asked for their consent.

The consent and randomisation forms will be emailed, to the SOLVE trial office, as these are the sole documents with identifiable details, again with consent from the woman. This will be used to perform in-house monitoring of the consent process. All data will be entered onto a secure computer database, either directly via the internet using secure socket layer encryption technology or indirectly form paper by BCTU staff.

The Investigator must maintain documents not for submission to the SOLVE trials office (e.g., Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

The SOLVE trial office will maintain the confidentiality of all participants' data and will not disclose information by which women may be identified to any third party, other than those directly involved in the treatment of the participant, and organisations for which the woman has given explicit consent for data transfer (e.g. competent authority, sponsor). Representatives of the SOLVE trial office and sponsor may be required to have access to participant's notes for quality assurance purposes but women should be reassured that their confidentiality will be respected at all times.

16 Insurance and indemnity

This is a clinician-initiated study. The Sponsor (BWCNFT) holds the relevant insurance for Clinical Trials (negligent harm). Participants may be able to claim compensation, if they can prove that the BWCNFT has been negligent. However, in terms of negligent liability, as this clinical trial is being carried out in a hospital setting, NHS Trust and Non-Trust Hospitals have a duty of care to the patients being treated within their hospital, whether or not a patient is participating in a clinical trial. Compensation is only available via NHS indemnity in the event of clinical negligence being proven. Women who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's R&D office. There are no specific arrangements for compensation made in respect of any SAE occurring though participation in the trial, whether from the side effects listed, or others yet unforeseen. Hospitals selected to participate in this trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary should be provided to BWCNFT, upon request.

The funder warrants that there is product liability insurance for DILAPAN-S®. Upon request, the funder shall provide evidence of such insurance. The funder has not arranged for any other insurance connected with the clinical trial.

17 Publication policy

Regular newsletters will keep collaborators informed of trial progress, and meetings will be held to report the progress of the trial and to address any problems encountered in the conduct of the trial.
The Chief Investigator will coordinate dissemination of data from this trial. The funder supports the exercise of academic freedom and encourages the Chief Investigator to publish the results of the clinical trial, whether or not the results are favourable to the funder or any funder's product. Accordingly, the Sponsor and the Chief Investigator will have the right to publish the results of the clinical trial. All publications and presentations, including abstracts, relating to the main trial will be authorised by the SOLVE TMG regarding the contents of the proposed presentation or publication, except as relates to the improper disclosure of confidential information. The results of the analysis will be submitted for publication, in the name of the SOLVE Collaborative Group, in a peer reviewed journal. All contributors to the trial will be listed, with their contribution identified. Abstracts will be submitted to international medical congresses.

Trial participants will be able to access the final results of the trial via the trial website, which will contain a reference to the full paper. All publications/presentations using data from this trial to undertake original analyses will be submitted to the TMG for review before release. These must be submitted in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. To safeguard the scientific integrity of the trial, data from this trial will not be presented in public before the main results are published without the prior consent of the TMG. Authors must acknowledge that the trial was performed with the support of the Sponsor (Birmingham Women's and Children's NHS Foundation Trust) and funded (Medicem Technology S.R.O).

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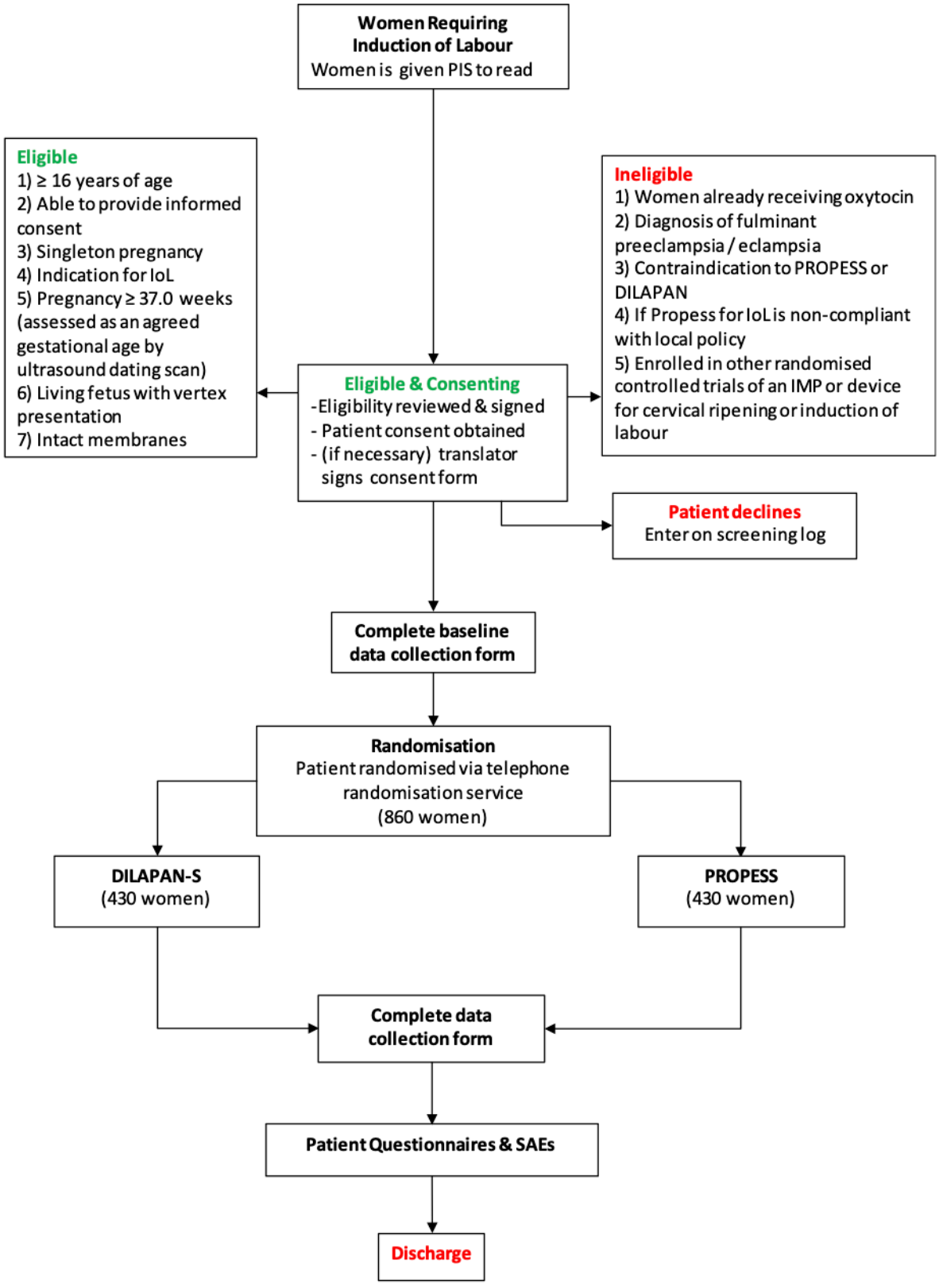
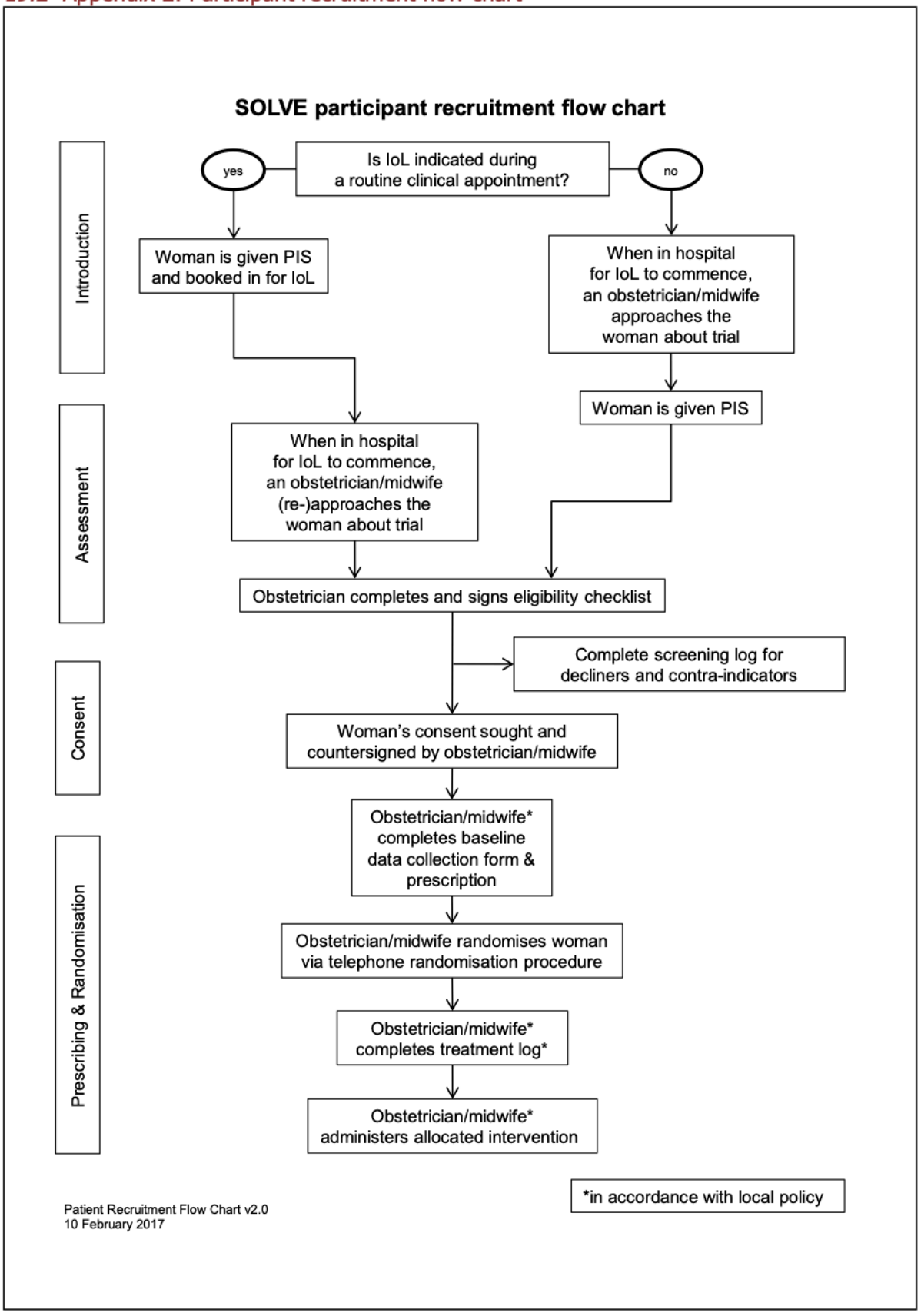
19 Appendices

19.1 Appendix 1: Trial Schema



19.2 Appendix 2: Participant recruitment flow chart



19.3 Appendix 3: Table of Responsibilities

Process	Time	Person Responsible
Confirm eligibility	**When IoL indicated**	**Full GCP AND targeted SOLVE trained obstetrician**
Consent	**Following confirmation of eligibility**	**Targeted SOLVE trained obstetrician or midwife**
Randomisation telephone call	**Following confirmation of consent**	**Targeted SOLVE trained obstetrician, midwife, student midwife or maternity support worker**
Prescription of treatment	**Following randomisation**	**Targeted SOLVE trained obstetrician**
Study treatment administration	**Following prescription**	**Targeted SOLVE trained midwife or obstetrician (check local NHS trust policy)**
Baseline & Birth data collection	**From randomisation until after birth**	**Targeted SOLVE trained midwife**
Maternal Satisfaction data collection	**Before discharge/transfer**	**Targeted SOLVE trained midwife**