1. CLINICAL STUDY PROTOCOL

OPTION – OutPatienT InductiON:

Labour induction in an outpatient setting - a multicentre randomized controlled trial.

Study code:	OPTION
EudraCT number:	2020-000233-41
Version number:	3.0
Date:	2020-07-06
Sponsor:	Sahlgrenska University Hospital, Gothenburg, Sweden Västra Götalandsregionen
Coordinating Principal Investigator	Verena Sengpiel

Table of contents

Signature page

Sponsor/Coordinating Principal Investigator

I am responsible for ensuring that this protocol includes all essential information to be able to conduct this study. I will submit this protocol and all other important study-related information to the staff members and responsible investigators who participate in this study, so that they can conduct the study correctly. I am aware of my responsibility to continuously keep the staff members and responsible investigators who work with this study informed and trained.

I have read this protocol and agree that it includes all essential information to be able to conduct the study. By signing my name below, I agree to conduct the study in compliance with this protocol, the Declaration of Helsinki, ICH GCP (Good Clinical Practice) guidelines and ISO14155, and the national and international regulations governing the conduct of this clinical study.

I am aware that quality control of this study will be performed in the form of monitoring, possibly audit, and possibly inspection.

2020-07-07

Sponsor/Coordinating Principal Investigator's signature — Date

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Printed name

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List of used acronymes and abbreviations

Abbreviation	Explanation
AE	Adverse Event

AR	Adverse Reaction = adverse event, that is each unfavourable and unexpected reaction to a study treatment, regardless of dose
BS	Bishop Score
BSE	Breastfeeding self-efficacy scale (questionnaire)
CEQ2	Childbirth experience questionnaire 2
eCRF	Electronic Case Report Form
EPM	Etikprövningsmyndigheten (English: Swedish Ethical Review Authority)
EQ-VAS	Euro-Qol Visual Analogue Scale (questionnaire)
EQ-5D	Euro-QOL 5 D– LIVSKVALITETSSKALA (questionnaire)
FTFQ	Father for the first time (questionnaire)
GCP	Good Clinical Practice
GSE	General Self Efficacy (questionnaire)
HAD	Hospital Anxiety and Depression Scale (questionnaire)
HRQL	Health-related quality of life (questionnaire)
ICH	International Council for Harmonisation
Induction	Induction of labour
ITT	Intention-to-treat
PCS	Pain catastrophizing scale (questionnaire)
PP	Per Protocol analysis
PROM	Premature rupture of the membranes
RCT	Randomized Controlled Trial
R-RCT	Register-based Randomized Controlled Trial
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SCB	Statistics Sweden
SNQ	Swedish Neonatal quality register
SOC-13	Sense of Coherence (questionnaire)
SPC or SmPC	Summary of Product Characteristics
SPR	Swedish Pregnancy Register

SUSAR	Suspected Unexpected Serious Adverse Reaction
USADE	Unanticipated Serious Adverse Device Effect
VD 24	Vaginal delivery within 24h
VD 48	Vaginal delivery within 48h

1. Synopsis

EudraCT number: 2020-000233-41
Title: OutPatienT InductiON Labour induction in an outpatient setting - a multicenter randomized controlled trial
Study code: OPTION
Short background/Rationale/Purpose: **Background**: The recently published SWEdish Post term Induction Study (SWEPIS) (1) showed increased perinatal mortality when late term pregnancies were induced at 42+0 weeks – current routine in Sweden – instead of at 41+0 weeks. The Swedish Society for Obstetrics and Gynaecology now recommends that women should be allowed to choose themselves whether they want to be induced at 41+0 weeks (https://www.sfog.se/start/om-sfog/aktuellt/nya-sfog-raad-om-induktion-paa-grund-av-graviditetslaengd/). As 22% of all women are still undelivered at week 41+0, few delivery units are able to offer this change of routine within the current organization. When labour starts spontaneously, women usually stay at home during the phase of cervical ripening and are admitted to the hospital upon entering active labour. How to induce labour depends on the status of the cervix. When the cervix is ripe, labour can be induced by artificial rupture of the membranes. Otherwise induction needs to start with cervical ripening, either by inserting a balloon catheter or by the use of prostaglandins. Few and small studies have investigated if induction by cervical ripening could be performed in an outpatient setting. None of these studies were powered to study safety aspects of the rare outcome of perinatal or maternal death or severe morbidity. Nor were the studies sufficiently large or homogenous to allow for a meta-analysis of safety outcomes. Nevertheless, some hospitals in other Scandinavian countries have introduced outpatient induction in clinical routine during recent years, with balloon catheter as well as with prostaglandins. At these hospitals, 42-75% of all inductions begin as outpatient induction. As a consequence of the result from the SWEPIS trial, many clinics in Sweden are now turning to outpatient induction as a solution to the demand of extra inductions at 41+0 weeks. However, as studies published on outpatient induction are underpowered for efficacy and especially the rare outcome of maternal and perinatal death or severe morbidity, the number needed to treat by induction in week 41+0 could be in the same range as the number needed to harm by outpatient induction. Therefore, outpatient induction should only be introduced in Sweden in the context of a clinical multicentre study. Studies on women´s experiences of outpatient induction described that the home environment resulted in physical and emotional comfort, which improved their birth experiences. Sense of security in pregnancy, childbirth and the postnatal period can depend on multiple internal and external factors, which can differ between mothers and fathers. Midwives in Australia experienced the introduction of outpatient induction as feasible. To our knowledge, there are no studies of the

partner's experiences of outpatient induction and no studies describing women's or healthcare staff experiences of outpatient induction in a Swedish setting.

Objective: To evaluate if induction of labour in an outpatient setting is non-inferior to induction in hospital in a low-risk population regarding safety for the child (composite outcome for neonatal morbidity and mortality) as well as regarding efficacy, defined as proportion of women with vaginal delivery. Further other pregnancy outcomes, the acceptability and experience of the woman, her partner and the staff, as well as future pregnancy outcome and health economic consequences will also be studied. Our hypothesis is that outpatient induction regardless of method, balloon catheter (Foley or Cook) or oral misoprostol, is non-inferior to inpatient induction in low-risk women regarding the two primary outcomes neonatal safety as well as efficacy measured as vaginal delivery.

Method: A national multicentre register-based parallel group randomized controlled trial (R-RCT) performed with support of the Swedish Network for clinical studies in Obstetrics and Gynaecology (SNAKS, www.snaks.se). The study will be run as an Register Randomised Controlled Trial (R-RCT) with randomization by the Swedish Pregnancy Register (SPR, www.graviditetsregistret.se) and data collection from SPR, the Swedish Neonatal Quality Register (SNQ, *Svenskt neonatalt kvalitetsregister*), the Swedish Ambulance Register, the Swedish Inpatient Register, the Cause of Death Register and Statistics Sweden (SCB). Secondary outcomes will also be collected from patient charts and in form of questionnaires based on validated instruments as well as interviews.

The trial will be conducted according to Good Clinical Practice (GCP) and the International Conference on Harmonization (ICH) guidelines. Approval from the Swedish Medical Products Agency and the Swedish Ethical Review Authority will be in place before trial start. The trial will be reported according to the CONSORT guidelines.

Eligible participants are healthy women between ≥37+0 and 41+6 gestational weeks with Bishop score <6 (<5 in parous women) planned for induction at one of the participating hospitals. Each centre will have a unique randomization list at a ratio of 1:1 with random permuted blocks. Randomization will be stratified for parity, indication for induction, and induction method.

Women will first have an abdominal palpation to exclude malpresentation, a cardiotocography (CTG), and a digital cervical exam to establish Bishop score prior to inclusion (as per clinical practice). After inclusion an ultrasound scan will be performed to exclude malpresentation, oligo- or polyhydramniosis and if indicated intrauterine growth restriction. Randomization will be performed after induction and an initial 45 min observation by the attending physician, midwife or study coordinator. Randomization only affects outpatient or inpatient care *and hence is not dependent of the method*. *The method is decided upon clinical basis*, either balloon catheter or oral misoprostol. The balloon catheter can either involve a Foley Catheter (Coloplast) or a Cook balloon. The Cook balloon is used according to its indications and hence this application does not involve the Cook balloon although used in the study. It can also involve oral misoprostol (Angusta®). Blinding is not

deemed feasible neither for the patient nor the investigator/site personal due to the character of the intervention (inpatient or outpatient care). During statistical analyses allocation will be blinded.

Inclusion criteria	**Exclusion criteria**
Based on medical history	
• women 18-45 years old • able to communicate with the hospital • uncomplicated live singleton pregnancy • pregnancy week ≥37+0 to 41+6 according to crown rump length (CRL) or biparietal diameter (BPD<55 mm) at first or second trimester ultrasound • *engaged and stable* cephalic presentation	• previous uterine surgery with uterine scar, e.g. caesarean section or myomectomy • pregestational or medically treated gestational diabetes (insulin or metformin) • dietary treated gestational diabetes with large for gestational age foetus • preeclampsia or instable hypertensive disease • multiple pregnancy • intrauterine foetal death (IUFD) in current or previous pregnancy • known foetal malformations or other foetal condition affecting the delivery or immediate care of the new-born • congenital uterine malformation which may affect safety • other condition requiring inpatient care, e.g. delivery within 60 min from arriving at the hospital in previous pregnancy • not able to reach the hospital in a reasonable time, at the discretion of the investigator with a maximum of 60 min as a benchmark (31)
Based on clinical examination before start of induction including Leopold´s manoeuvres, digital cervical exam, abdominal ultrasound, temperature, blood pressure and CTG scan	
• *engaged and stable* cephalic presentation with • Bishop score <6 (<5 in parous women) • CTG classified as normal according to the antepartal Swedish Society of Obstetrics and Gynaecology (Svensk Förening för Obstetrik och Gynekologi, SFOG) criteria (www.ctgutbildning.se)	• Small for gestational age (SGA/IUGR/FGA) Screened for as follows depending on the indication for induction: 1. late term ≥41+0 to 41+6 weeks: abdominal ultrasound will be performed and mean abdominal diameter (MAD) needs to be ≥110 mm In case MAD <110 mm, the foetal weight will be estimated to exclude SGA foetus defined as <2 standard deviation according to Marsal et al (32) 2. dietary treated gestational diabetes or stable hypertension: foetal weight estimated by abdominal ultrasound within the last two weeks before induction and showing no SGA defined as <2 standard deviation according to Marsal et al (32) 3. prolonged latent phase, maternal age, mild intrahepatic cholestasis, pelvic girdle pain, PROM, psychosocial:

	Normal fundal height measurement according to the Swedish reference curves is needed In case of not-normal fundal height measurement: foetal weight estimation must be performed and showing no SGA defined as <2 standard deviation according to Marsal et al (32) 4. Other indications: at the discretion of the investigator • Oligohydramniosis: deepest vertical pocket <20 mm or amniotic fluid index <50 mm • polyhydramniosis: if head not engaged or amniotic fluid index >300 mm • maternal pyrexia ≥38°C • known low-lying placenta (less than 20 mm from internal os measured by vaginal ultrasound in week 36) • high head (≥4/5 palpable abdominally) Regarding premature rupture of membranes (PROM) • PROM is exclusion criteria for balloon method • PROM is exclusion criteria for prostaglandin method if: o PROM >30 hours o Known colonisation with group B streptococci or previous pregnancy complication linked to group B streptococci
Based on observation the first 45 min after start of induction	
• in case of induction with balloon method: CTG classified as normal according to the antepartal Swedish Society of Obstetrics and Gynaecology (Svensk Förening för Obstetrik och Gynekologi, SFOG) criteria (www.ctgutbildning.se)	• any adverse events within the first 45 min after start of induction, e.g. heavy bleeding, pain, PROM in case PROM was not indication for induction of labour • start of contractions

Power and feasibility:
Two primary outcomes have been defined: a composite outcome for neonatal morbidity and mortality as well as an efficacy outcome defined as proportion of women with a vaginal delivery. Further pregnancy outcomes, the acceptability and experience of the woman, her partner and the staff, as well as future pregnancy outcome and health care economics will also be studied. Non-inferiority will be tested with a two-sided 95% confidence interval and 80% power. Given 2.8% in outpatients and 2.3% in inpatients for the primary composite variable and a 5% drop-out rate, we need to randomize **8891 women** in order to achieve a probability ≥0.80 that the upper limit of a two-sided 95.7% confidence interval (CI) for the difference in primary outcome will be less than the non-inferiority margin 1.5%. Based on the number of inductions at the participating sites, we expect that

recruitment could be achieved within 2.5 years. The register-based follow-up is planned for 10 years after the last delivery.

Study design

<table>
<tr><th>Visit (timepoint)</th><th colspan="3">1

(Day 1)</th><th>2

(Day 2, at the latest 24 hours after induction)</th><th>3

(Day 3, at the latest 24 hours after visit 2)</th><th>X

At interims analysis and at final analysis of study data</th><th>X

(3 months after delivery)</th><th>X

(10 years after delivery)</th></tr>
<tr><td rowspan="6"></td><td colspan="3" rowspan="2">1. Medical history taken (clinical routine)

2. Standard examination before induction including CTG scan, confirming foetal presentation, (Leopold´s manoeuvres), digital cervical exam, blood pressure and temperature control (clinical routine)

3. Inclusion

4. Abdominal ultrasound as indicated

5. Induction of delivery, choice of method according to clinical routine (except that only specified products in this application can be chosen)

6. 45 min observation at the hospital, CTG in case of balloon catheter and woman (and partner) answers electronical OPTION questionnaire

7. Randomization</td><td colspan="3">Treatment A, Hospital induction:

Woman is admitted to the hospital upon inclusion and stays at the hospital until delivery</td><td>Data collection on primary and secondary outcomes by registers</td><td rowspan="6">Woman (and partner) answers electronical OPTION questionnaire

(no visit)</td><td rowspan="6">Data collection on longterm follow-up by registers

(no visit)</td></tr>
<tr><td>Treatment B,

Outpatient induction:

Woman returns home or to a patient hospital</td><td colspan="2">Treatment B, in case of indication for induction was:</td><td></td></tr>
<tr><td colspan="2">1) PROM*: Woman is admitted to the hospital if not delivered yet and stays at the hospital until delivery</td><td>N=4445

(or 2119 in each arm and induced with each method – balloon or oral prostaglandin)</td></tr>
<tr><td colspan="2">2) Other than PROM*:</td><td rowspan="2">N=4445

(or 2119 in each arm and induced with each method – balloon or oral prostaglandin)</td></tr>
<tr><td>Another day of outpatient induction if not delivered yet and reassuring clinical examination including CTG, confirming foetal presentation, blood pressure and temperature control.</td><td>Admission to hospital for continued induction if not delivered yet</td></tr>
</table>

*PROM premature rupture of the membranes

Investigational product(s), dosage, administration:

The placenta position and the position of the fetus is checked by vaginal ultrasound to ensure occiput position of the fetus and no placenta praevia. After that a Foley catheter (Coloplast AB6H22) will be inserted through the cervix and the balloon will be inflated with 50 ml of NaCl and the position of the balloon will be at the cervical internal os checked by ultrasound. A CTG must be normal prior to putting the balloon in place and also after the balloon is in place. The balloon will be position here for a maximum of 24 hours.

Up to eight doses of 25microgram misoprostol tablets taken orally no closer than 2 hours apart/24 hours, for a maximum of 2 days. On day 3 (if relevant), all women return to clinical routine at study sites. Intake can be paused during the night. Intake can also start with 24 hours of Angusta® and then a switch to Foley catheter might be applicable.

Study outcomes:

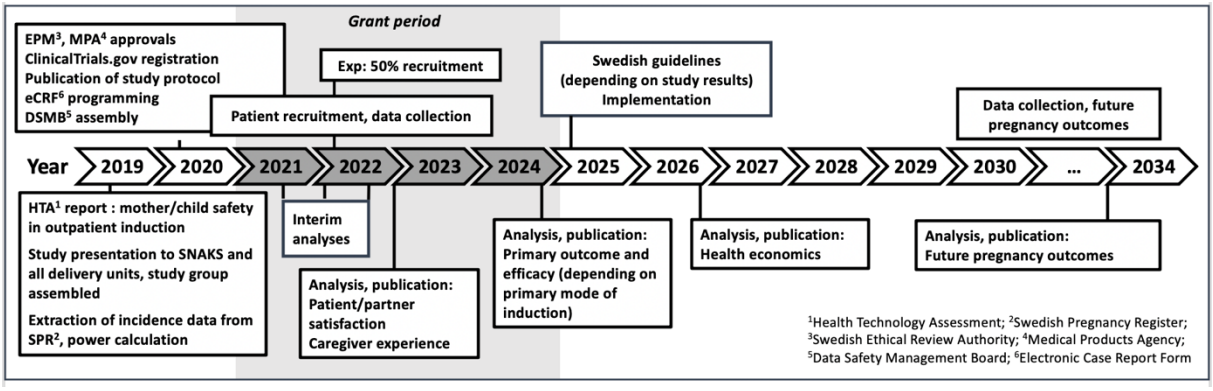
Primary variable: Two primary outcome variables have been defined.

1) A primary safety neonatal composite outcome defined as one of the following: Stillbirth defined as intrauterine foetal death of a foetus that was alive at time of randomization, Neonatal death of a live born child that dies day 0-27, not including accidents or lethal malformation not known before randomization, Apgar score <4 at 5 minutes, pH <7.00 or base deficit >15 mmol/l in the umbilical artery, Hypoxic ischaemic encephalopathy I-III, Intracranial haemorrhage, Neonatal convulsions, Therapeutic hypothermia, Meconium aspiration syndrome, Mechanical ventilation within first 72 hours, Neonatal pneumonia, Neonatal sepsis, NICU admission >48 hours duration.

2) A primary efficacy outcome, defined as proportion of women with vaginal delivery.

Secondary variable(s): Further pregnancy outcomes, the acceptability and experience of the woman, her partner and the staff, as well as future pregnancy outcome and health economic consequences will also be studied.

Study period:



2. Background and rationale

The recently published SWEdish Post term Induction Study (SWEPIS) showed a higher perinatal mortality when late term pregnancies are induced at 42+0 weeks – which is current routine in Sweden – instead of at 41+0 weeks (1). The Swedish Society for Obstetrics and Gynaecology (SFOG) now recommends that women should be offered to choose themselves whether they want to be induced in week 41+0 https://www.sfog.se/start/om-sfog/aktuellt/nya-sfog-raad-om-induktion-paa-grund-av-graviditetslaengd/. The mean induction rate in Sweden before SWEPIS was published was 19% in 2018. In 2018 6,1% reached 42+0 or later. As 22% of all women are still undelivered at week 41+0, few delivery units are able to offer this change of routine within the current organization.

When labour starts spontaneously, women usually stay at home during the phase of cervical ripening and are admitted to the hospital upon entering active labour. How to induce labour depends on the status of the cervix. When the cervix is ripe, labour can be induced by amniotomy. Otherwise induction is initiated by cervical ripening, either by inserting a balloon catheter or the use of oral or vaginal prostaglandins. The National Institute for Health Care and Excellence (NICE) guidelines states that: “In the outpatient setting, induction of labour should only be carried out if safety and support procedures are in place” and “The practice of induction of labour in an outpatient setting should be audited continuously” (https://www.nice.org.uk/guidance/cg70/chapter/1-Guidance#setting-and-timing).

However, few studies have tested if induction by cervical ripening could be safely performed in an outpatient setting, and of those that have studied this, none were powered to study the rare outcome of severe child or maternal morbidity or death (2-9). Some hospitals in other Scandinavian countries have introduced outpatient induction in clinical routine during recent years. At these hospitals 42-75% of all induction are started as outpatient induction (10) (personal communication). In the light of the SWEPIS result, currently many clinics in Sweden turn to outpatient induction as a solution for the demand for induction at 41+0 weeks.

Traditionally, induction is monitored in the hospital setting as induction agents have the potential to initiate uterine activity, sometimes hypercontractility or even uterine rupture. Non-reassuring foetal heart rate resulting in caesarean sections, foetal distress and in rare cases perinatal death can be the consequences. Further, infectious complications for mother and child have been linked to induction (11). A meta-analysis by Diederen et al (n= 8,292 women) showed, however, that there were few complications related specifically to the phase of cervical ripening with a balloon catheter regardless of in- or outpatient setting. Pain/discomfort was the most common symptom experienced (12). A retrospective study (n=1,905) reported no adverse outcomes among low risk pregnancies during cervical ripening with a balloon catheter (13). A retrospective study on outpatient induction with a balloon catheter in Helsinki, Finland, indicated no increased risk for adverse maternal or child outcome (n=204) (10). Low-dose oral misoprostol is considered one of the safest methods for

induction and a recommended first line alternative (14). While previous studies on induction with either balloon methods or prostaglandins indicate low risk during the phase of cervical ripening, which would be the time that could be spent in an outpatient setting; no RCT testing the outpatient setting was powered to study the rare outcome of severe perinatal or maternal morbidity or death (2-9). Nor were individual studies sufficiently large or homogenous to allow for a meta-analysis of safety outcomes. The latest Cochrane reviews ask specifically for further research regarding safety and efficacy of outpatient induction (2, 15). Thus, the number needed to treat by induction in week 41+0 could be in the same range as the number needed to harm by outpatient induction.

Apart from safety aspects, possible effects of outpatient induction on experience for both the women, their partners as well as medical staff need to be considered. Midwives in Australia experienced the introduction of outpatient induction as feasible (16). A cross-sectional study in 2005 of 450 women at term undergoing hospital induction with cervical ripening and 450 women labouring spontaneously showed that labour that was artificially induced resulted in lower satisfaction rates as compared to that following spontaneous onset. The time delay between the start of the induction and the delivery played a significant part in this, with the mode of administration of the inducing agent and more vaginal examinations being perceived as secondary issues. The authors concluded that there is a need for improvement regarding the information provided to women undergoing induction in order to counter unrealistic expectations and thereby improve satisfaction (17). Also, two systematic reviews of qualitative evidence on women's perceptions and experience of hospital induction identified several negative experiences e.g., the amount of information, delays in starting and progress of induction, pain and pain relief and the women's perceptions of choice and involvement in decision-making during induction (18). Studies on women´s experiences of outpatient induction described that the home environment resulted in physical and emotional comfort, which helped women cope better with their labour and improved their birth experiences (19, 20). A recent integrative literature review concluded that sense of security in pregnancy, childbirth and the postnatal period can depend on multiple internal and external factors, which can differ between mothers and fathers and that further research focused on the experiences of security from the parents' perspective is necessary (21). A qualitative interview study described that feelings of safety within the home environment were perceived by clear written instructions about what to expect after going home, a 24 h ability to call and talk with a midwife for any reason, and ensurement that they could come back to the hospital at any time (22, 23). Women also identified the importance to have support from their husband/partner (22).

Becoming a father is one of the most life-changing events a man can experience, suggesting it is imperative to understand the father's perinatal experiences and their possible consequences (24). However, studies of fathers/partners childbirth experience are scarce. A literature review of 62 studies from 2000 to 2015, found that despite fathers attendance at births in Scandinavian countries is becoming more the rule rather than the exception (98%) (25), men still do not receive the support they need and want from perinatal health professionals, which consequently makes them unprepared for the experience of birth and fatherhood (26). Findings also suggest that traumatic births can have a profound impact on some fathers, which can ultimately negatively impact their relationship with their partner, bounding with their new child and their own mental health (27).

Screening to identify fathers who are most at risk of poor mental health is recommended; and services to ensure fathers receive appropriate support for their own mental health need to be developed. To our knowledge, there are no studies of the partner's experiences of outpatient induction yet and no studies describing women's or healthcare staff experiences of outpatient induction in a Swedish setting.

Further, outpatient induction may be more cost-effective. In Australia, Adelson et al found that outpatient induction had the potential to save $156 per woman compared to induction at the hospital, though the results were not significant (28). Son et al concluded that outpatient induction with balloon is cost reducing, especially when time on the labour department is shortened by more than 3.5 hours (29). A study from the Netherlands estimated a €670 cost reduction per woman in case of outpatient compared to inpatient induction with a balloon catheter (30).

In summary, outpatient induction might be a way to offer a communicative and patient-centred approach and thus an option to increase patient satisfaction and shared decision-making. At the same time, outpatient induction has the potential to reduce the cost of induction and free up resources for other patients. However, as long as safety of outpatient induction for the mother and foetus/neonate is not established, outpatient induction should not be offered as clinical routine but introduced in form of a clinical multicentre study in the Swedish healthcare system. The timing for a study like this is just right as all delivery units need to overlook their routines in light of the recent SWEPIS results.

3. Risk-benefit evaluation

1. Women who are planned for induction are at the end of a pregnancy and have been thinking about delivery for many months. While most are happy to meet their child soon, some might be worried for their own and their child's health. In this situation women have to be approached in a careful manner regarding study participation.

- Only women planned for induction considered as low-risk as defined in the study protocol, will be approached.
- Participating women will receive oral and written information in different languages and must give written consent prior to inclusion.
- Women should be given time to make a decision and there should be no pressure to participate.
- The women can withdraw their participation at any time without further explanation and without consequences for their medical care.
- Women are considered solely responsible for the foetus as long as it is inside the womb. Thus, care must be taken that the woman herself makes the decision to participate and is not pressured by her partner's or the healthcare staff's opinion.

2. Partners do not need to consent to the pregnant women participating in the study. However, partners to pregnant women are invited to participate in the partner part of the study.

- We believe that a balanced information can be given in a calm environment.
- Participating partners will receive oral and written information in different languages or give their informed consent prior to inclusion.
- Partners should be given time to make a decision and there should be no pressure to participate.
- The partners can withdraw their participation at any time without further explanation and without consequences for their pregnant partners medical care. However, it is the pregnant woman's decision whether she wants to participate in the OPTION trial.

3. The stage of induction at which women might stay at home is called cervical ripening. Risks for the foetus during cervical ripening are very low. Cervical ripening by induction mimics the natural process during which most women without induction stay home. Induction will be achieved by established and well-documented methods; both Foley and Cook Catheter and Angusta® have been used for many years for induction at the hospital and have also been used for out-patient care but not yet with enough power to detect seldom outcomes such as neonatal outcome. While outpatient induction has not previously been offered in Sweden, it is clinical routine in e.g. the other Nordic countries (Denmark and Finland). However, risks with outpatient induction cannot be ruled out, which is why this study is undertaken. The risks include fetal distress, bleeding, pain or maternal infection during unsupervised contractions and at a longer distance from immediate medical attention. These risks should be balanced against a possible risk of hospital induction linked to a higher degree of medically unmotivated interventions. Outpatient induction has the potential to increase patient – and partner – satisfaction. Women are often exhausted by apprehension and loss of sleep during induction. Earlier research (19, 20) has found that women are less satisfied after induction as compared to spontaneous onset of delivery. The time delay between start of induction and delivery being most important, with mode of administration of the inducing agent and vaginal examinations being perceived as secondary issues. Furthermore, women miss involvement in decision-making during induction. Outpatient induction has been shown to increase physical and emotional comfort, which helped women cope better with labour and improved their birth experiences (19, 20).

- Only women with low-risk inductions are eligible for this study.
- In addition to standard care, participating women will be examined with an abdominal ultrasound to identify conditions unsuitable for outpatient induction.
- All women get written and oral information to call back if the feel any change whatsoever. **Please note separate patient information.** If misoprostol is the method of choice, they will continue oral misoprostol 25 μg no closer than every two hours, up to eight doses per 24 hours. The hospital will provide a written scheme on when to take the remaining doses of misoprostol. The scheme may allow sleep during night-time. If Cook balloon is the method of choice the women will return to hospital after a maximum 12 hours according to the instructions from the manufacturer. If the Foley catheter will be used they will return for a clinical control and withdrawal of the balloon after a maximum 24 hours.

- Women will contact the 24/7 hospital telephone line to a midwife trained to answer the phone for advice and in case of complications, questions or start of delivery. At the last after 24 hours (12 hours in case of Cook balloon) has passed after start of induction, they will return to the hospital on a booked appointment for further planning of induction according to clinical practice, see below.
- In case of severe complications at home, e.g. major vaginal bleeding, the women will be advised to come to the hospital by ambulance just as women with spontaneous onset of delivery.
- In the case of a severe adverse event occurring in either group, women and their partners will get support and care by specialised healthcare professionals as established in clinical routine.

4. Adverse effects linked to insertion of the balloon catheter

Balloon catheters have been used for induction of delivery since years. Expected adverse effects are discomfort comparable to discomfort experienced by women with spontaneous onset of delivery during the latency phases.

- Study participants will be offered pain killers in form of oral medication.

The balloon catheter might be misplaced in the vagina instead of the cervix.

- A vaginal ultrasound will be performed after balloon insertion to confirm correct placement.
- In case wrong placement is not detected, the only expected adverse effect is delayed induction.

The balloon catheter placement can cause the water to break

- The balloon can either stay in place and the patient will be excluded from the study, or the balloon catheter will be removed, the women will be induced with Angusta® instead and can be randomized.

The balloon might come apart which is a very rare event.

- The balloon will be removed immediately and a new balloon will be placed or the induction method is changed to Angusta®.

The fetus changes from head to breech position which has been described in rare occasions.

- Only women with a stable cephalic position are eligible.
- The balloon will be filled with only 50 ml.
- The fetus position will be assessed at each visit to the hospital.
- In case of breech presentation at a second control, hence the baby has turned during induction the patient will stay in-hospital and handled according to clinical praxis.

5. Adverse effects linked to intake of Angusta®

In rare occasions hyperstimulation has been described.

- Women at risk for uterine rupture due to earlier surgery on the uterus are not eligible.
- Women will stay at the hospital for 45 min after the first tablet of Angusta® in order to identify women that might react strongly to the medication. In case of strong reactions, these women are not eligible for randomization.
- A low dose regime with only 25 μg Angusta® orally every second hour is applied. Women are informed both orally and written that they should not take the next tablet in case of more contractions or tension in the uterus but to contact the hospital.

6. Data safety:

Data will be collected from various registers, patient charts, questionnaires and interviews and personal data will be encoded so that individuals cannot be identified in the analysis.

The researchers have no financial interest in the study. Results will be published in open access peer-reviewed journals and presented at national and international conferences. The public will be informed on the study results through public media and the study homepage.

5. In case safety, efficacy, acceptability, and cost effectiveness can be established, outpatient induction can free healthcare resources for other women with a greater need for care.

It is our baiting assessment that the risks with using well-known methods for induction at home are far less than the advantages it would mean both for mother and child, for the pregnant population as a whole and for the Swedish health care setting, to be able for the pregnant mother to be in their home environment during the start-up phase of delivery just as they are when the delivery starts naturally.

6. Regarding the COVID-19 pandemic, delivery department are waiting for this study to start as the study will immediately free resources at the delivery departments, resources that are desperately needed now that rooms and facilities cannot be used as usual due to contagiousness as well as constant lack of staff.

As women (and partners) in the outpatient group spend more time at home, we expect less risk for this group to become infected by contact with staff or other patients being positive for SRAS-CoV-2. Women and partners participating in the OPTION study will be asked to self-isolate at home during the time of induction spent as outpatients in order to minimize risk for infection during this additional days at home. From admission to the hospital, study participants will have to follow the same rules as applicable for all other patients and partners as well.

4. Study objectives

The aim of this study is to evaluate if induction of labour (induction) in an outpatient setting is ***non-inferior*** to induction in hospital in a low risk population regarding 1) safety for the child (composite outcome) as well as 2) efficacy defined as proportion of women with a vaginal delivery. Further other

pregnancy outcomes, the acceptability and experience and of the woman, her partner and staff, as well as health economic consequences will be compared between the two groups. Furthermore, number, mode of delivery, and pregnancy outcomes in subsequent pregnancies will be followed.

Outpatient induction is already performed in several countries including Sweden, although studies showing safety for the child as well as the mother are lacking.

4.1. Primary objective

The primary objective of the study is to show if outpatient induction is as safe and as effective as inpatient induction.

4.2. Secondary objective(s)

Secondary objectives of the study are to answer the following research questions:

Efficacy and health care costs:

- Do the proportions of vaginal delivery (VD) in each group, VD within 24 and 48h from start of induction (VD24, VD48), and induction-to-delivery interval (hours), total hours in hospital, number of visits, telephone calls, need for ambulance transport, number of subsequent pregnancies, and mode of delivery in future pregnancies differ between the outpatient and inpatient group?
- Is outpatient induction cost-effective compared with inpatient induction?

Acceptability:

- Does outpatient induction differ from inpatient induction with respect to acceptability in patients, partners, and healthcare staff?
- How do women and their partner experience induction of labour at home i.e. out-patient induction?
- How do women and their partner experience induction of labour at the hospital i.e. inpatient induction?
- Does acceptability of induction of labour differ between women and partners in the outpatient and inpatient groups?
- Does induction of labour differ between women and partners in the outpatient and inpatient groups?
- How does medical health staff experience outpatient induction?

4.3. Primary variable

Primary health outcomes:
Pregnancy and delivery related outcomes will be retrieved by the SPR, SNQ, the Cause of death register the Cause of death register and SCB according to the following table. Data regarding postpartum complication will be collected from the Swedish inpatient register. Outcomes are specified according to the recommendations in the latest Cochrane report on outpatient induction

(39) as well as the crown initiative core outcome set for induction (40) as far as possible with regard to the register-based manner of data retrieval.

1) The primary safety outcome is a composite variable for perinatal mortality and neonatal morbidity.

2) The primary efficacy outcome is defined as proportion of women with vaginal birth.

The primary variables are described in more detail in section 8.1.1, Primary variable

4.4. Secondary variable(s)

Secondary variables are described in more detail in section 8.1.2, Secondary variable(s).

4.4.1. The woman's experience of outpatient versus inpatient induction

Women will answer electronical questionnaires directly after induction but before randomization as well as three months after delivery.

Women with low-risk induction experiences of induction in an outpatient setting and in a hospital setting will be measured by comparison of general self-efficacy (GSE), health-related quality of life (HRQL, EQ-VAS, EQ-5D), Sense of Coherence (SOC-13), pain catastrophizing (PCS), anxiety and depression (HAD) before randomization.

The GSE, EQ-VAS, EQ-5D, SOC, PSC, HAD, EPDS, Childbirth experience 2 (CEQ2) and levels of breastfeeding (BES) will be measured 3 months after delivery.

Also, experience of the induction management will be evaluated by a questionnaire adapted from Bollapragada et al.

Questionnaires will be sent through a link via e-mail and/or SMS three months after delivery. The questionnaires will be eligible in Swedish. When validated translations of the instruments exist, these will be available even in other languages. Questions specifically developed for OPTION will be translated to other languages as well.

For all women, satisfaction with delivery will also be studied as registered in the SPR: After delivery all women delivering in Sweden are supposed to be asked how satisfied they are with their delivery rating from 1 (not satisfied) to 10 (satisfied). The proportion of women with experience rated as >7 and <4 will be compared between groups.

4.4.2. The women's partner's experience of induction of labour in an outpatient versus inpatient setting

Womens' partners will answer electronical questionnaires directly after induction but before randomization of their partner as well as three months after delivery.

Background characteristics as age, education level, number of children and number experiences of childbirths and induction of labour will be registered. The partners experiences of their pregnant

partner's induction in an outpatient setting and in a hospital setting will be measured by comparison of general self-efficacy (GSE), health-related quality of life (HRQL, EQ-VAS, EQ-5D), Sense of Coherence (SOC-13), pain catastrophizing (PCS), anxiety and depression (HADS) before randomization as well as three months after delivery. EPDS and childbirth experience (Father for The First time questionnaire (FTFQ)) will be measured, analyzed and compared between groups three months after delivery (49). The FTFQ consists of 22 items rated on a four-point Likert scale assessing the father's/partner's experience of childbirth in four dimensions; worry, information, emotional support, and acceptance. Each dimension is evaluated separately using the mean score for the dimension as the result (range 1-4, where a lower score represents a better experience). No total score is calculated.

The questionnaires will be sent through a link via e-mail and/or SMS. When validated translations of the instruments exist, these will be available even in other languages. Questions specifically developed for OPTION will be translated to other languages as well.

4.4.3. Women's and their partners' experience of outpatient versus inpatient induction

A total of 15 -20 women and 15-20 partners will be interviewed 3-6 months after delivery. It could be either the woman or the partner or both that will be interviewed.

Informants will be selected to ensure a broad range of views and experiences of the phenomenon outpatient induction, e.g. age, parity and socio-economic background. For further description see below.

4.4.4. Care givers experience of outpatient induction

The phenomenon outpatient induction will be studied regarding the health care professionals' experience about six months after the introduction of outpatient induction at the Sahlgrenska University Hospital Gothenburg (and other sites that want to join the sub-study). Healthcare staff (n=20) will be chosen strategically according to age, gender, and profession (midwife, doctor), as well as working place (answering the phone, working at the induction unit, working at the delivery unit, working in postnatal care). Healthcare staff will be asked regarding their experience of working with low-risk women induced in an outpatient setting as compared to low-risk women induced at the hospital.

Data collection and data analysis for the interview part

The women, the partners and the health care professional respectively will receive both oral and written information and will be informed of the purpose and voluntary nature of the study. They will be assured that the data will be treated confidentially and that they are free to withdraw at any time. They in turn will give their written consent before answering the questionnaires or taking part in the interview.

Interviews will be conducted at the hospital or in the woman's/partner's/health care professional's home, depending on their preference. The informants will be interviewed separately. Face-to face interviews (50, 51) will be performed by a member of the research group or a research

assistant/midwife. An open–ended question will be used “Please tell me of your experience of outpatient induction’’. Follow-up questions such as “How did that feel” and “Can you please tell me more,” will also be asked to deepen understanding. The interviewer will create an open climate to enable the informant to find the right words to express her/his experiences (52). Interviews will last approximately 1 h and will be audiotaped and transcribed verbatim. Data analysis will be conducted by either phenomenology with a lifeworld approach (53) or content analysis (50). NVivo8 software will be used to code and review categories (https://www.qsrinternational.com/).

4.4.5. Health economics

The following will be monitored: pregnancy, child, and maternal outcome including time from induction to delivery (hours, SPR, patient chart), time in the delivery unit (hours, SPR, patient chart), the number of calls to the midwife after start of induction (patient chart). Mode of delivery; spontaneous vaginal birth, instrumental vaginal birth, or caesarean section (SPR). Time from induction to active labour (SPR). Primary method of induction (SPR). If other method of induction is needed (SPR, patient chart). Duration of stay at hospital after delivery (SPR). Need of revisit postpartum (SPR, patient chart, the inpatient register). Readmission postpartum within the first month (SPR, patient chart, the inpatient register). Number and reasons of visits and phone calls to the hospital in the outpatient group (balloon expulsion, planned visit before and after 24 h, PROM, pain, vaginal bleeding, contractions, impaired urination, foetal movements, delivery before reaching the hospital, other) will be monitored at certain centres as these data are not available from the SPR, but from regional registers and/or patient charts.

4.4.6. Future deliveries

In a register-based follow-up study 10 years after the initial study based on SPR data, number of future deliveries, mode of delivery, fear of childbirth, and patient satisfaction will be studied by linkage to the personal identification number. This part of the study is register-based only. No further study visits are planned after discharge from the hospital after delivery.

5. Study design and procedures

5.1. Overall study design

A national multicentre register-based parallel group randomized controlled trial (R-RCT) (phase IV) within the Swedish Network for clinical studies in Obstetrics and Gynaecology (SNAKS, www.snaks.se). The study will be run as a R-RCT with randomization by the Swedish Pregnancy Register (SPR, www.graviditetsregistret.se) and data collection from SPR, Swedish Neonatal Quality Register (SNQ, *Svenskt neonatalt kvalitetsregister*), the Swedish Ambulance Register, the Swedish Inpatient Register, the Cause of Death Register and Statistics Sweden (SCB). Secondary outcomes will also be collected from patient charts and in form of questionnaires based on validated instruments as well as interviews.

The study will be performed with a ***non-inferiority design*** regarding the primary composite outcome of perinatal safety as well as the efficacy outcome defined as women with a vaginal delivery.

The trial will be conducted according to Good Clinical Practice (GCP) and the International Conference on Harmonization (ICH) guidelines and ISO14155. Approval from the Swedish Medical Products Agency and the Swedish Ethical Review Authority will be in place before trial start. The trial will be registered at clinicaltrials.gov and reported according to the CONSORT guidelines.

5.2. Patients

Eligible participants are healthy women between ≥37+0 and 41+6 gestational weeks with a modified Bishop score <6 (<5 in parous women) planned for induction at one of the participating hospitals.

Table 1. Modified Bishop score: Sum of grades for 5 different parameters (0 most unfavourable)

Bishop score	**0**	**1**	**2**
Station of foetal head	above/at pelvic entrance	above/at spines	below spines
Cervical position	posterior	mid-line	anterior
Cervical Consistency	firm	moderately firm	soft (ripe)
Cervical Effacement	maintained	<50%	>50%
Cervical Dilation	<0.5 cm	0.5 – 1.5 cm	1.5 cm

Women should be willing and able to comply with the protocol and able to understand oral and written information in Swedish or able to give their informed consent with the help of a translator. Written information about the study will be provided in different languages. However, the woman needs to be able to reliably communicate with the healthcare staff by telephone, e.g. with help of relatives or friends. Also, the woman's health should be good enough for her to have been able to stay at home if she would have had a spontaneous onset of labour.

5.3. Possible indication for induction

Possible - but not exclusive - indications for induction are:

- late term: ≥41+0 to 41+6 weeks according to crown rump length (CRL) or biparietal diameter (BPD <55 mm) at first or second trimester ultrasound (abdominal ultrasound will be performed and mean abdominal diameter (MAD) needs to be ≥110 mm at gestational week ≥41+0 to 41+6)
- dietary treated gestational diabetes without large for gestational age foetus (estimated foetal weight by abdominal ultrasound during the last two weeks needs to be within normal range)
- large for gestational age/macrosomia without diabetes diagnosis
- stable hypertensive disease defined as chronic hypertensive disease or gestational hypertension with blood pressure <140/90 without or with medication. In case of medication: no need for

increase of medication during the last week and an estimated foetal weight by abdominal ultrasound during the last two weeks without suspicious small for gestational age (SGA) diagnosis

The following indications for induction are possible in case of antenatal fundal height measurements are normal. Otherwise abdominal ultrasound will be performed to rule out fetal growth restriction:

- prolonged latent phase
- maternal age according to local routine
- mild intrahepatic cholestasis with serum bile acids <40 µmol/L
- pregnancy-related pelvic girdle pain
- premature rupture of membranes <30 hours (for prostaglandin method only)
- induction of labour without medical reason (psychosocial)
- other at the discretion of the investigator

5.4. In- and exclusion criteria, fit for randomization

All inclusion criteria and none of the exclusion criteria based on medical history and clinical examination need to be fulfilled in order for a woman to be ***included into the study***.

All inclusion criteria and none of the exclusion criteria based on medical history, clinical examination, abdominal ultrasound and observation the first 45 min after start of induction need to be fulfilled in order for a woman to be ***randomized***.

Note that randomization is performed *as late as possible* in the process as the big drop out between early randomization and intervention was a major limitation identified in earlier studies on this topic, meaning that there were huge differences between the intention to treat and the per protocol population complicating the interpretation of the results.

Table 2 Inclusion and exclusion criteria, fit for randomization

Inclusion criteria	**Exclusion criteria**
Based on medical history	
• women 18-45 years old • able to communicate with the hospital • uncomplicated live singleton pregnancy • pregnancy week ≥37+0 to 41+6 according to crown rump length (CRL) or biparietal diameter (BPD<55 mm) at first or second trimester ultrasound • *engaged and stable* cephalic presentation	• previous uterine surgery with uterine scar, e.g. caesarean section or myomectomy • pregestational or medically treated gestational diabetes (insulin or metformin) • dietary treated gestational diabetes with large for gestational age foetus • preeclampsia or instable hypertensive disease • multiple pregnancy • intrauterine foetal death (IUFD) in current or previous pregnancy • known foetal malformations or other foetal condition affecting the delivery or immediate care of the new-born

	• congenital uterine malformation which may affect safety • other condition requiring inpatient care, e.g. delivery within 60 min from arriving at the hospital in previous pregnancy • not able to reach the hospital in a reasonable time, at the discretion of the investigator with a maximum of 60 min as a benchmark (31)
Based on clinical examination before start of induction including Leopold´s manoeuvres, digital cervical exam, abdominal ultrasound, temperature, blood pressure and CTG scan	
• *engaged and stable* cephalic presentation with • Bishop score <6 (<5 in parous women) • CTG classified as normal according to the antepartal Swedish Society of Obstetrics and Gynaecology (Svensk Förening för Obstetrik och Gynekologi, SFOG) criteria (www.ctgutbildning.se)	• Small for gestational age (SGA/IUGR/FGA) Screened for as follows depending on the indication for induction: 5. late term ≥41+0 to 41+6 weeks: abdominal ultrasound will be performed and mean abdominal diameter (MAD) needs to be ≥110 mm In case MAD <110 mm, the foetal weight will be estimated to exclude SGA foetus defined as <2 standard deviation according to Marsal et al (32) 6. dietary treated gestational diabetes or stable hypertension: foetal weight estimated by abdominal ultrasound within the last two weeks before induction and showing no SGA defined as <2 standard deviation according to Marsal et al (32) 7. prolonged latent phase, maternal age, mild intrahepatic cholestasis, pelvic girdle pain, PROM, psychosocial: Normal fundal height measurement according to the Swedish reference curves is needed In case of not-normal fundal height measurement: foetal weight estimation must be performed and showing no SGA defined as <2 standard deviation according to Marsal et al (32) 8. Other indications: at the discretion of the investigator • Oligohydramniosis: deepest vertical pocket <20 mm or amniotic fluid index <50 mm • polyhydramniosis: if head not engaged or amniotic fluid index >300 mm • maternal pyrexia ≥38°C • known low-lying placenta (less than 20 mm from internal os measured by vaginal ultrasound in week 36) • high head (≥4/5 palpable abdominally)

	Regarding premature rupture of membranes (PROM):
	• PROM is exclusion criteria for balloon method
	• PROM is exclusion criteria for prostaglandin method if:
	  ○ PROM >30 hours
	  ○ Known colonisation with group B streptococci or previous pregnancy complication linked to group B streptococci

Based on observation the first 45 min after start of induction	
• in case of induction with balloon method: CTG classified as normal according to the antepartal Swedish Society of Obstetrics and Gynaecology (Svensk Förening för Obstetrik och Gynekologi, SFOG) criteria (www.ctgutbildning.se)	• any adverse events within the first 45 min after start of induction, e.g. heavy bleeding, pain, PROM in case PROM was not indication for induction of labour • start of contractions

According to the PICO model- for clinical questions (population, intervention, control, outcome)

Population: Low-risk pregnant women with an unripe cervix (Bishop score <6 in nulliparous or <5 in parous women) planned for induction between gestational week ≥37+0 and 41+6 fulfilling all inclusion criteria and without any of the exclusion criteria, willing to and able to comply with the protocol.

Before randomization, women have received either a balloon catheter (Foley catheter or Cook® Cervical Ripening Balloon) or the first dose of 25 μg misoprostol orally (Angusta®). Participating hospitals need to be familiar with the misoprostol preparation used before entering the study, recommended at least one month's clinical experience.) in the hospital. The method has been chosen depending on clinical practice at the study site, the doctors judgement and woman's choice and follows the guidelines from the Swedish Society of Obstetrics and Gynaecology (SFOG) (33). In case of PROM, induction with Angusta® is the only method accepted in this protocol. A CTG has been performed in case of balloon catheter after placement of the catheter. If no immediate adverse events have occurred within the first 45 min after start of induction, women will be randomized to either outpatient or inpatient setting and if allocated to outpatient setting sent home or to a patient hotel.

Intervention: Outpatient induction with either balloon catheter or Angusta®.

If misoprostol was chosen as induction method, women will continue oral Angusta® 25 μg no closer than every two hours, up to eight doses per 24 hours. The hospital will provide a written scheme on when to take the remaining doses of misoprostol. The scheme may allow sleep during night-time and the women will continue with Angusta® after she wakes up.

Women will contact the 24/7 telephone line at their hospital and talk to a midwife trained to answer the phone for advice and in case of complications or start of delivery. At the last after 24 hours has passed after start of induction (12 hours in case of Cook® balloon) they will return to the hospital on a booked appointment for further planning of induction according to the table below.

Control: Inpatient induction with either balloon catheter or oral prostaglandin.

If allocated to inpatient setting women will stay at an induction/antenatal care unit or the delivery unit depending on the hospital's routine. The balloon will be handled according to the hospital's routine. In case of Angusta® was chosen as induction method, a tablet of 25 μg misoprostol orally (Angusta®) will be administered no closer than every two hours, up to eight doses per 24 hours. The scheme may allow sleep during night-time. Thereafter induction will proceed according to the table below.

Outcome: The two primary outcomes are 1) a composite outcome of severe perinatal morbidity or mortality and 2) efficacy defined as proportion of women with vaginal delivery. Secondary outcomes include further neonatal and maternal outcomes, the women's, partners' and caregivers' experience, health care costs, as well as outcomes regarding future pregnancies.

5.5. Inclusion and randomization procedure

Women will be informed on the study by information in waiting areas in the hospital or antenatal care unit (posters and pamphlets), social media, the hospitals homepages and parent education. Preferably, all women receive written information on the study in conjunction with booking time for induction of labour.

When the woman arrives at the hospital, a standard medical history will be taken to establish eligibility including a review of the fundal height chart. The foetus position will be defined by Leopold´s manoeuvres. A CTG will be done and a midwife or doctor will perform a digital cervical exam to establish the Bishop score. The clinical examination further includes a blood pressure and temperature control.

The woman will receive oral and written information on the study by the clinical or research staff at the study site. If the woman is eligible and gives her informed written consent, her data will be entered into the electronical case report from (eCRF) linked to the Swedish Pregnancy Register. An abdominal ultrasound will be performed to exclude oligohydramnios, polyhydramniosis, and malpresentation and in cases specified above SGA/FGR. Induction will be initiated as described in the PICO. The woman (and her partner) will fill in electronical questionnaires. In case of no adverse event within the first 45 min after initiation of induction and a normal CTG in case of induction with balloon catheter, the study participant will be randomized by a randomization module linked to the SPR.

Randomization will take place in a module developed within the SPR easily accessed through the computer using the SITHS-card. Each centre will have a unique randomization list at a ratio of 1:1

with varying block size. Randomization will be stratified by 1) indication for induction (PROM – not PROM), 2) parity (nulliparous – parous), and 3) induction method (balloon catheter – oral prostaglandin) within each centre. The attending physician, midwife or study coordinator is responsible for the information, inclusion, signing of informed consent, and randomization. Blinding is not deemed feasible for neither the woman and partner, the clinical or research staff; however, randomization will be performed after the woman has been induced and monitored for 45 min after induction so that choice of method and initial monitoring after induction cannot be affected by group allocation.

Date and time for induction as well as tick boxes for "main" and "secondary indication for induction" with the following choices will be added to the eCRF as indication for induction is not reliably available from the SPR:

- late term ≥41+0 to 41+6 weeks
- dietary treated gestational diabetes without macrosomia
- stable hypertension (gestational or essential)
- large for gestational age/macrosomia without diabetes diagnosis
- prolonged latent phase, number of whole hours
- maternal age
- mild intrahepatic cholestasis with serum bile acids <40 µmol/L
- pregnancy-related pelvic girdle pain
- premature rupture of membranes (for prostaglandin method only)
- induction of labor without medical reason (psychosocial)
- other, specify (free text)

Time to hospital in minutes according to the woman's estimation and whether the woman will stay in a patient hotel (defined as no interventions or surveillance available) will be recorded in the eCRF.

Women who have given consent to participation, but are excluded before randomization due to resulting exclusion criteria after examination and/or induction, will be registered in the eCRF and the reason for exclusion will be marked in tick boxes:

- SGA according to ultrasound examination
- Oligohydramniosis according to ultrasound examination
- Polyhydramniosis with AFI >300 mm
- Foetal malformation affecting delivery or immediate care for the neonate
- Low-lying placenta according to ultrasound examination
- Start of contractions
- Premature rupture of the membranes (in case PROM was not indication for induction)
- Severe bleeding (at the discretion of the physician)
- Pain – more than expected discomfort (at the discretion of the physician)
- Fever
- CTG not classified as normal
- Withdrawal
- Other, specify (free text)

5.6. Treatment

Participating women will be induced as described in the PICO. Possible methods are induction with a balloon catheter in form of 1) Cook (according to approved indication in FASS) or 2) Foley (Coloplast) or oral misoprostol in form of 3) Angusta®. Choice of induction method is not specified by the study protocol other than one of the three above needs to be chosen and will be performed according to clinical routine. However, in case of indication for induction is PROM, Angusta® is the only method of induction in this trial. All women regardless of randomized to outpatient or inpatient induction will be offered pain relief (oral paracetamol or paracetamol in combination with a morphine analogue, no codeine).

If the woman is not delivered within the first 24 hours (12 hours in case of Cook® balloon) a change of method is possible according to the following:

- In case of PROM only oral Angusta® can be used for induction.
- A balloon catheter can only be used once for a maximum of 12 hours in case of the Cook® balloon and for a maximum of 24 hours for the Foley catheter.
- Angusta® can be used according to the scheme specified in the PICO for two days within this study protocol.
- Induction/augmentation of labour with oxytocin infusion may start earliest 4 hours after the last dose of misoprostol due to the risk of hyperstimulation.
- In case a woman is not delivered the third day, the responsible clinician and the woman can decide upon the induction method according to the hospital's routine which might include the same and/or different methods of induction than specified in this protocol. At this time all women have been admitted to the hospital and return to clinical routine.

If available, women allocated to outpatient induction can be offered to stay at a patient hotel. As such, outpatient induction is defined as the woman staying in a place without access to immediate surveillance or delivery and where the woman needs to be transferred to the hospital in case of adverse event or active labour.

5.7. Surveillance and follow-up of the study participants during induction

Inpatient induction: Monitoring will be performed according to the participating hospitals' routine. Hospital routines will be collected and published as supplemental material.

Outpatient induction: Each participating hospital provides a 24/7 telephone line to a midwife trained to answer the phone who will answer to women with outpatient induction. Women are informed to monitor foetal movements as usual and asked to contact the hospital immediately in case of any of the following symptoms. In case of induction with oral misoprostol they should stop intake until contact with the hospital:

- if anything feels different from when the woman was sent home
- start of contractions
- rupture of the membranes (unless PROM was the reason for induction)
- in case of PROM: any change in amniotic fluid colour
- in case the balloon catheter comes out
- sudden change/decrease in foetal movements
- bleeding
- continuous abdominal pain
- fever
- the woman feeling unsure about something

Choice/change of induction method (for both groups) and follow-up visits in the outpatient group is planned as follows:

1) In case of indication for induction is *not* PROM a maximum of 2 days can be spent in the outpatient setting, with clinical control at least every 24 hours after induction (12 hours in case of Cook® balloon).

Table 3.1 Surveillance and follow-up in case indication for induction is not premature rupture of the membranes

<table>
<tr><th>Day 1 – outpatient</th><th colspan="2">Day 2 – outpatient</th><th colspan="2">Day 3 – inpatient</th></tr>
<tr><td></td><td colspan="2">Visit 2

Clinical examination including CTG, confirming foetal presentation, blood pressure and temperature control.

If reassuring findings, regular contractions have not started and amniotomy is not possible:</td><td colspan="2">Admission to the hospital

Induction continues according clinical routine at the study site.</td></tr>
<tr><td colspan="5">Method for induction</td></tr>
<tr><td colspan="5">Choice and change of method within the study protocol or decision to stop/pause induction may be made due to clinical routine, the clinician’s judgement, and/or the woman’s preference, however:

• Balloon catheter can only be applied once during the induction process.
• In case of misoprostol day 1 and 2, change of method is recommended day 3.
• Induction/augmentation of labour with oxytocin infusion may start earliest 4 hours after the last dose of misoprostol due to the risk of hyperstimulation.</td></tr>
<tr><td colspan="5">Treatment</td></tr>
<tr><td>Balloon catheter</td><td>Angusta®
Up to eight doses of 25 μg misoprostol tablets taken orally no closer than 2 hours apart/24 hours.</td><td>Balloon catheter</td><td>Angusta®
Up to eight doses of 25 μg misoprostol tablets taken orally no closer than 2 hours apart/24 hours.</td><td>Induction continues according clinical routine at the study site which may include the same and/or other methods than specified in this protocol.</td></tr>
</table>

	Intake can be paused during the night.		Intake can be paused during the night.	Follow-up and surveillance according to clinical routine.
Immediate surveillance at the hospital				
After balloon application CTG 45 min and observation at the hospital	After first tablet (dose 1) in the hospital 45 min observation at the hospital, time schedule for the next seven doses (dose 2-8) at home	After balloon application CTG 45 min and observation at the hospital	After first tablet (dose 1) in the hospital 45 min observation at the hospital, time schedule for the next seven doses (dose 2-8) at home	
Information before going home				
Oral and written information on when to contact the hospital, booked time for follow-up after a maximum of 24 hours (12 hours in case of Cook balloon)				

2) In case of indication for induction is PROM **a maximum of 1 day** can be spent in the outpatient setting.

Table 3.2 Surveillance and follow-up in case indication for induction is premature rupture of the membranes

Day 1 - outpatient	**Day 2 - *inpatient***
	Admission to the hospital Induction continues according to clinical routine at the study site.
Method for induction	
Choice and change of method within the study protocol or decision to stop/pause induction may be made due to clinical routine, the clinician's judgement, and/or the woman's preference, however: Induction/augmentation of labour with oxytocin infusion may start earliest 4 hours after the last dosage of misoprostol due to the risk of hyperstimulation.	
Treatment	Induction continues according clinical routine at the study site which may include the same and/or other methods than specified in this protocol. Follow-up and surveillance according to clinical routine.
Angusta® Up to eight doses of 25 μg misoprostol tablets taken orally no closer than 2 hours apart/24 hours. Intake can be paused during the night.	
Immediate surveillance at the hospital	
After first tablet (dose 1) in the hospital 45 min observation at the hospital, time	

schedule for the next seven doses (dose 2-8) at home	
Information before going home	
Oral and written information on when to contact the hospital, booked time for follow-up after a maximum of 24 hours	

Study design

Table 4 Overview over the study design

Visit (timepoint)	**1** **(Day 1)**		**2** **(Day 2, at the latest 24 hours after induction)**	**3** **(Day 3, at the latest 24 hours after visit 2)**	**X** **At interims analysis and at final analysis of study data**	**X** **(3 months after delivery)**	**X** **(10 years after delivery)**
	1. Medical history taken (clinical routine) 2. Standard examination before induction including CTG scan, confirming foetal presentation, (Leopold´s manoeuvres), digital cervical exam, blood pressure and temperature control (clinical routine) 3. Inclusion 4. Abdominal ultrasound as indicated 5. Induction of delivery, choice of method according to clinical routine (except that only specified products in this application can be chosen)	Treatment A, Hospital induction: Woman is admitted to the hospital upon inclusion and stays at the hospital until delivery			Data collection on primary and secondary outcomes by registers	Woman (and partner) answers electronical OPTION questionnaire (no visit)	Data collection on longterm follow-up by registers (no visit)
		Treatment B, Outpatient induction: Woman returns home or to a patient hospital	Treatment B, in case of indication for induction was:				
			1) PROM*: Woman is admitted to the hospital if not delivered yet and stays at the hospital until delivery		N=4445 (or 2119 in each arm and induced with each method – balloon or oral prostaglandin)		
			2) Other than PROM*:		N=4445 (or 2119 in each arm and induced with each method – balloon or oral prostaglandin)		
			Another day of outpatient induction if not delivered yet and reassuring clinical examination including	Admission to hospital for continued induction if not delivered yet			

	6. 45 min observation at the hospital, CTG in case of balloon catheter and woman (and partner) answers electronical OPTION questionnaire 7. Randomization		CTG, confirming foetal presentation, blood pressure and temperature control.				

*PROM premature rupture of the membranes

5.8. Procedures and flow chart

Table 5 Study procedure and flow chart

Procedure	*Screening Day 1 Inclusion visit 1*	*Visit 2* *Day 2 (max 24 hours after induction, max 12 hours in case of Cook balloon)* Only outpatient group (Inpatient group stays at the hospital)	*Visit 3* *Day 3 (max 24 hours after Visit 2, max 12 hours in case of Cook balloon)* Only outpatient group (Inpatient group stays at the hospital)	Until 42 days after delivery (no visit)	After 3 months + 2 weeks (no visit)
Incl/exclusion criteria	√	√	√		
Standard clinical examination	√	√	√		

before induction including CTG scan, confirming foetal presentation, (Leopold´s manoeuvres), digital cervical exam, blood pressure and temperature control (clinical routine)					
Informed consent	√				
Abdominal ultrasound as indicated	√				
Randomization	√				
Questionnaire *Woman: GSE, HRQL, EQ-VAS, EQ-5D, SOC-13, PCS, HAD, freetext* *Partner: GSE, HRQL, EQ-VAS, EQ-5D, SOC-13, PCS, HAD, freetext*	√				√
Questionnaire *Woman: EPDS, CEQ2, BES, questions adapted from*					√

Bollapragada, freetext *Partner: EPDS, FTFQ, questions adapted from Bollapragada, freetext*					
Instruction for continued induction and when to contact the hospital in case not delivered yet	√	√	√		
Continued induction in case not delivered yet		√	√		
Adverse Events (AE & SAE)	√	√	√	√	
Study end					√

5.9. Biological sampling procedures

5.9.1. Handling, storage, and destruction of biological samples

N/A

5.9.2. Total volume of blood per study subject

N/A

5.9.3. Biobank

N/A

5.10. End of Study

Primary outcome includes neonatal death up to 28 days.

SAE includes maternal death up to 42 days after delivery as well as re-admission to hospital due to serious events such as pulmonary embolism and sepsis after delivery within 42 days.

Questionaries' will be sent out after 3 months plus 2 weeks.

Data on future pregnancy outcome will be collected from registers only 10 years after delivery.

Data and the data key will be kept for 20 years to guarantee long-time follow-up of the mothers and children.

The active part of the study ends when the last study participant has completed the last follow-up (3 months).

The study may be prematurely terminated if it appears that the treatment involved a large number of undesirable serious events or if recruitment of study participants cannot be met within reasonable time limits. If the study is prematurely terminated or suspended, the investigator should immediately inform the study participants about this and ensure appropriate treatment and follow-up. The regulatory authority should be informed as soon as possible, but no later than within 15 days.

Decisions on premature termination are taken by the sponsor, after advice from the DSMB.

6. Subject selection

Study participants are part of the study as follows:

- Until maximum day 3 after start of induction as study participants that receive different treatment than usual – only if randomized to the outpatient group.
- Until day 42 SAE will be reported.
- After three months plus 2 weeks an electronic questionnaire will be answered.
- After 10 years from the delivery date, data will be collected on future pregnancy outcome for long-term follow-up.

6.1. Inclusion criteria

To be included in the study, subjects must meet the following criteria:

Eligible participants are healthy women between ≥37+0 and 41+6 gestational weeks with a modified Bishop score <6 (<5 in parous women) planned for induction at one of the participating hospitals.

The subject has given written consent to participate in the study.

Women should be willing and able to comply with the protocol and able to understand oral and written information in Swedish or able to give their informed consent with the help of a translator. Written information about the study will be provided in different languages. However, the woman needs to be able to reliably communicate with the healthcare staff by telephone, e.g. with help of relatives or friends. Also, the woman's health should be good enough for her to have been able to stay at home if she would have had a spontaneous onset of labour.

For detailed inclusion and exclusion criteria, see "Table 2 Inclusion and exclusion criteria, fit for randomization" in section 5.4 "In- and exclusion criteria, fit for randomization".

6.2. Exclusion criteria

Subjects must not be included in the study if any of the criteria stated in section 5.4 are met, including that the woman needs to be able to reliably communicate with the healthcare staff by telephone, e.g. with help of relatives or friends. Also, the woman's health should be good enough for her to have been able to stay at home if she would have had a spontaneous onset of labour.

For detailed inclusion and exclusion criteria, see "Table 2 Inclusion and exclusion criteria, fit for randomization" in section 5.4 "In- and exclusion criteria, fit for randomization".

6.3. Screening

Subject eligibility is established in several steps:

All inclusion criteria and none of the exclusion criteria based on medical history and clinical examination need to be fulfilled in order for a woman to be ***included into the study***.

All inclusion criteria and none of the exclusion criteria based on medical history, clinical examination, abdominal ultrasound and observation the first 45 min after start of induction need to be fulfilled in order for a woman to be ***randomized***.

Note that randomization is performed *as late as possible* in the process as the big drop out between early randomization and intervention was a major limitation identified in earlier studies on this topic, meaning that there were huge differences between the intention to treat and the per protocol population complicating the interpretation of the results.

6.4. Withdrawal criteria

Withdrawal criteria after randomization:

1) The woman presents with an exclusion criterion or the responsible researcher becomes aware of an exclusion criterion during the course of induction:

- previous uterine surgery with uterine scar, e.g. caesarean section or myomectomy
- pregestational or medically treated gestational diabetes (insulin or metformin)

- dietary treated gestational diabetes with large for gestational age foetus
- preeclampsia or instable hypertensive disease
- multiple pregnancy
- intrauterine foetal death (IUFD) in current or previous pregnancy
- known foetal malformations or other foetal condition affecting the delivery or immediate care of the new-born
- congenital uterine malformation which may affect safety
- other condition requiring inpatient care, e.g. delivery within 60 min from arriving at the hospital in previous pregnancy
- not able to reach the hospital in a reasonable time, at the discretion of the investigator with a maximum of 60 min as a benchmark (31)

2) Subjects can discontinue their participation in the study at any time without any consequence to his/her continued treatment except that women in the outpatient arm have to be admitted to the hospital and proceed with induction as inpatients according to clinical routine.

3) The investigator/sponsor can at any time terminate the study for a subject due to, e.g., unacceptable adverse events/adverse reactions or because the subject does not follow procedures in the study protocol.

If the subject discontinues the study, follow-up of this subject will be performed according to the clinic's routine. In either case, serious adverse events will be followed up.

Other reasons for discontinuing a subject are incorrect enrolment and subjects lost to follow-up. Loss to follow-up is deemed as practically impossible as women will give birth within a few days from randomization and data will be collected by the SPR independent on where the woman will give birth.

Women who have given consent to participation, but are excluded before randomization due to resulting exclusion criteria after examination, will be registered in the eCRF and the reason for exclusion will be marked in tick boxes:

- SGA according to ultrasound examination
- Oligohydramniosis according to ultrasound examination
- Polyhydramniosis with AFI >300 mm
- Foetal malformation affecting delivery or immediate care for the neonate
- Low-lying placenta according to ultrasound examination
- Start of contractions
- PROM (in case PROM was not indication for induction)
- Severe bleeding (at the discretion of the physician)
- Pain – more than expected discomfort (at the discretion of the physician)
- Fever
- CTG not classified as normal
- Withdrawal
- Other, specify (free text)

The study will continue until at least 8891 women have been randomized including until 2119 women have been randomized in each arm induced with balloon catheter or oral misoprostol (Angusta®), respectively. This is in order to have power to study the efficacy outcome (vaginal delivery) in the subgroups of women induced with balloon catheter as well as prostaglandin alone. At each participating study site at least 3 patients and at most all patients eligible for the study can be included.

The primary analysis and the first secondary analysis are non-inferiority analyses and hence analysed according to both ITT population and Per Protocol population. The only women who will be excluded from the Per Protocol analysis will be women who do not consent to go home after randomization. Women who e.g. experience rupture of the membranes after randomization but before leaving the hospital or women who might experience contractions or bleeding on their way home will be analysed in the outpatient group even in the Per Protocol analyses as admission of these women is part of the protocol.

An “as treated” analysis will be performed analysing women randomized to the outpatient group, but remaining inpatient due to not consenting to the outpatient setting in the inpatient group. No women in the inpatient group have the possibility to cross over to the outpatient group.

7. Study treatments

7.1. Description of investigational product(s)

Foley catether Coloplast X-FLOW® Prostatectomy short catheter straight tip 3-way 30-50 ml silicone CH FR 22 REF. AB6H22

Manufacturer: Coloplast

Please see the IB brochure for details.

A maximum of 24 hours in use.

The balloon will be ordered from Coloplast and stickers will be attached by Coloplast prior to distribution.

Participating hospitals are used to applying Foley catheters for induction – a standard procedure performed in daily routine at all delivery units since over 20 years. The objective of this study is not to study the medical technical device but induction in an outpatient setting.

Angusta®

Tablett 25 microgram misoprostol 8 tablett(er) Blister

Varunummer: 044492

Tillverkare: Azanta Danmark A/S

Please see FASS-text.

Up to eight doses of 25microgram misoprostol tablets taken orally no closer than 2 hours apart/24 hours, for a maximum of 2 days. On day 3 (if relevant), all women return to clincial routine at study sites. Intake can be paused during the night. Intake can also start with 24 hours of Angusta® and then a switch to Foley catheter might be applicable.
Angusta® is ordered from the pharmacy

7.2. Dose and administration

The Foley catheter is used for induction of labour placing it at the interval cervical os for a maximum of 24 hours.

The drug is used according to the instructions provided by FASS except that intake in the outpatient group will be at home/in a patient hotel after the initial tablet.

7.3. Packaging, labelling, and handling of investigational products(s)

The Foley catheter will be ordered from Coloplast and stickers will be attached by Coloplast prior to distribution.

The batch number will be noted in the eCRF for each patient.

Angusta® will be ordered from the Pharmacy and stored according to the manufacturer. No sticker will be applied. The number of doses as well as time-point for intake is documented in the patient information and later noted in the eCRF, together with the batch number. An accountability logg will not be used since the study drug as well as the Foley catheter are used according to clinical routine and the effect of the study drug as well as the Foley catheter are not the topic under investigation but the setting of induction – inpatient or outpatient. As the batch number will be noted in the eCRF for all patients, it will be available for investigation in case of possible SAE.

7.4. Drug accountability and treatment compliance

7.4.1. Foley catheter

The placenta position and the position of the foetus is checked by vaginal ultrasound to ensure occiput position of the foetus and no praevia. After that a Foley catheter will be inserted through the cervix and the balloon will be inflated with 50 ml of NaCl and the position of the balloon will be at the cervical internal os checked by ultrasound. A CTG must be normal prior to putting the balloon in place and also after the balloon is in place. The balloon will be position here for a maximum of 24 hours. The patient will get oral and written information on how to act at home and she will have access through telephone to an experienced midwife 24/7. The time-point when she enters the hospital again will be noted. If the waters breaks when putting the balloon catheter into place the woman and physician can either chose to leave the catheter in place and the woman will be excluded from the study before randomization or the catheter is removed, the woman receives Angusta® instead and can be randomized.

7.4.2. Angusta®

The patient will take the first Angusta® tablet in hospital after randomization and stay for 45 minutes before returning home. The patient will get oral and written information on how to take the rest of the tablets provided and she will have access through telephone to an experienced midwife 24/7. Some patients will take them at home and some at the hospital depending on randomization. Times for taking the tablets and missed doses will be noted in the patient information and later transferred to the eCRF for both groups.

7.5. Randomization

Subjects are included/randomized consecutively as they are found to be eligible for inclusion in the study. If a subject discontinues their study participation, their subject code will not be reused and the subject will not be allowed to re-enter the study again – if not with a new pregnancy and induction.

The Swedish Pregnancy Register (SPR) will be used for randomization and data registration through an attached electronic Case Report Form (eCRF) specifically developed for the study by MedSciNet AB, Stockholm, Sweden. An OPTION database will be established via MedSciNet, the platform for the SPR and SNQ. MedSciNet has experience setting up eCRF and databases like this from e.g. the SWEPIS (1) and CDC4G study (35). Data from the different registries, the eCRF and the questionnaires will be linked through the personal identification number and afterwards replaced by a studyID.

Randomization will take place in a module developed within the Pregnancy register easily accessed through the computer using the SITHS-card. Each centre will have a unique randomization list at a ratio of 1:1 with varying block size. Randomization will be stratified by 1) indication for induction (PROM – not PROM), 2) parity (nulliparous – parous), and 3) induction method (balloon catheter – oral prostaglandin) within each centre. The attending physician, midwife or study coordinator is responsible for the information, inclusion and signing of informed consent, and randomization. Blinding is not deemed feasible for neither patient, partner, clinical or research staff; however, randomization will be performed after the woman has been induced and monitored for 45 min after induction so that choice of method and monitoring cannot be affected by group allocation.

7.6. Blinding

N/A

7.7. Code breaking

N/A

7.8. Concomitant medications

All women regardless of randomized to outpatient or inpatient induction will be offered pain relief (oral paracetamol or paracetamol in combination with a morphine analogue, no codeine).

Medications that are considered necessary for the safety and well-being of the subject and/or her unborn child can be given at the discretion of the investigator, unless otherwise specified as an exclusion criterion.

7.9. Destruction

After use the material will be destroyed according to clinical routine.

7.10. Treatment after study end

N/A

8. Assessment of efficacy and safety

8.1. Assessment of clinical efficacy

Please see section 4.3

The pregnancy register as well as other registries will be used for outcome measurements. Vaginal delivery will be used for efficacy.

8.1.1. Primary variable

Table 6 Primary outcome variables

Primary outcome 1 is a composite variable for severe child morbidity and mortality including any of the following:			
Variable	**Type**	**Description**	**Source**

Stillbirth defined as intrauterine foetal death of a foetus that was alive at time of randomization	Dichotomous (yes, no)	Tick box, ICD-10 O36.4	SPR
Neonatal death of a live born child that dies day 0-27, not including accidents or lethal malformation not known before randomization	Dichotomous (yes, no)	SNQ 2101, 2103	SNQ, SCB, the Cause of death register
Apgar score <4 at 5 minutes	Dichotomous (yes, no)	SNQ 421, SPR ”Apgar 5”	SNQ, SPR
pH <7.00 or base deficit >15 mmol/l in the umbilical artery	Dichotomous (yes, no)		SNQ, SPR
Hypoxic ischaemic encephalopathy I-III	Dichotomous (yes, no)	P91.6 or P91.0 or tick box	SNQ
Intracranial haemorrhage	Dichotomous (yes, no)	P10, P52	SNQ
Neonatal convulsions	Dichotomous (yes, no)	P90	SNQ
Therapeutic hypothermia	Dichotomous (yes, no)	DV034	SPR, SNQ
Meconium aspiration syndrome	Dichotomous (yes, no)	P24.0	SNQ, SPR
Mechanical ventilation within first 72 hours	Dichotomous (yes, no)	DG021, DG022, DG002	SNQ
Neonatal pneumonia	Dichotomous (yes, no)	P23	SNQ
Neonatal sepsis	Dichotomous (yes, no)	P36	SNQ
NICU admission >48 hours duration	Dichotomous (yes, no)		SNQ
Primary outcome 2 is the efficacy variable defined as proportion of vaginal birth in the two groups			
Caesarean section	Dichotomous (yes, no)	Tick box ICD-10 O82 MCA00, MCA10, MCA20, MCA30, MCA33, MCA96	SPR
Vaginal delivery (spontaneous and instrumental)	Dichotomous (yes, no)	Tick box Spontaneous vaginal ICD-10 O80 Instrumental vaginal ICD-10 O81 MAF00, MAF10, MAF96, MAC23 MAE00, MAE03, MAE20, MAE96	SPR

8.1.2. Secondary variable(s)

8.1.2.1. Secondary health outcomes

Table 7 Secondary health outcome variables

Secondary outcome variables			
The different variables being part of the primary safety composite outcome will even be studied individually in form of exploratory analyses.			
Variable	**Type**	**Description**	**Source**
Stillbirth defined as intrauterine foetal death of a foetus that was alive at time of randomization	Dichotomous (yes, no)	ICD-10 O36.4	SPR
Neonatal death of a live born child that dies day 0-27, not including accidents	Dichotomous (yes, no)	SNQ 2101, 2103	SNQ, SCB, the Cause of death register
Apgar score <4 at 5 minutes	Dichotomous (yes, no)	SNQ 421, SPR ”Apgar5”	SNQ, SPR
pH<7.00 or base deficit >15 mmol/l in the umbilical artery	Dichotomous (yes, no)		SNQ, SPR
Severe birth asphyxia	Dichotomous (yes, no)	P21.0	SNQ, SPR
Hypoxic ischaemic encephalopathy II-III	Dichotomous (yes, no)	P91.6B or C or tick box	SNQ
Intracranial haemorrhage	Dichotomous (yes, no)	P10, P52	SNQ
Neonatal convulsions	Dichotomous (yes, no)	P90	SNQ
Therapeutic hypothermia	Dichotomous (yes, no)	P80.8, P80.9, DV034	SPR, SNQ
Meconium aspiration syndrome	Dichotomous (yes, no)	P24.0	SNQ, SPR
Mechanical ventilation within first 72 hours	Dichotomous (yes, no)	DG021, DG022, DG002	SNQ
Neonatal pneumonia	Dichotomous (yes, no)	P23	SNQ
Neonatal sepsis	Dichotomous (yes, no)	P36	SNQ
NICU admission >48 hours	Dichotomous (yes, no)		SNQ

Further outcomes for the child			
Obstetric brachial plexus injury	Dichotomous (yes, no)	P14.0, P14.1, P14.3, P14.8, P14.9	SNQ, SPR
Admission to the NICU	Dichotomous (yes, no)		SNQ
Time at NICU	Continuous (days and hours)		SNQ
Treatment for hypoglycaemia	Dichotomous (yes, no)	ICD-10 P70.3 P70.4A-B, P70.8, P70.9,	SNQ, SPR
Re-admission after delivery due to the child's health until day 27 after delivery	Dichotomous (yes, no)		SNQ
Healthy person accompanying sick person (Mother stays at the hospital due to need of care for the new-born) until day 27 after delivery	Dichotomous (yes, no)	ICD-10 Z76.3	SPR
Apgar score <7 at 5 minutes	Dichotomous (yes, no)	SNQ 241, SPR "Apgar5"	SNQ, SPR
Further outcomes for the mother			
Vaginal delivery (spontaneous vs instrumental)	Dichotomous (yes, no)	Tick box Spontaneous vaginal ICD-10 O80 Instrumental vaginal ICD-10 O81 MAF00, MAF10, MAF96, MAC23 MAE00, MAE03, MAE20, MAE96	SPR
Maternal death until 42 days after delivery that can be connected to the pregnancy	Dichotomous (yes, no)	ICD-10 O95, O97	SPR, SCB, the Cause of death register
Maternal death after 42 days after delivery that can be connected to the pregnancy	Dichotomous (yes, no)	ICD-10 O96	SPR, SCB, the Cause of death register
Preeclampsia	Dichotomous (yes, no)	ICD-10 O14, O15,	SPR
Gestational [pregnancy-induced] hypertension without significant proteinuria	Dichotomous (yes, no)	ICD-10 O13, O16	SPR
Precipitate labour	Dichotomous (yes, no)	ICD-10 O62.3	SPR
Hypertonic, incoordinate and prolonged uterine contractions	Dichotomous (yes, no)	ICD-10 O62.4	SPR
Uterine rupture	Dichotomous (yes, no)	ICD-10 O71.0, O71.1, KVÅ MCC00	SPR

Hysterectomy in connection with delivery	Dichotomous (yes, no)	ICD-10 O82.2, KVÅ MCA33,	SPR
Cardiac arrest	Dichotomous (yes, no)	ICD-10 I46	SPR, the Swedish inpatient register
Obstetric chock	Dichotomous (yes, no)	ICD O75.1	SPR
Other severe maternal morbidity defined as admission to intensive care unit	Dichotomous (yes, no)	ICD-10 ZV049	SPR, hospital charts, the Swedish inpatient register
Thrombosis, pulmonary embolism	Dichotomous (yes, no)	ICD-10 O22.3, O87.1, O87.3, I82.2, I82.8, I82.9, I26	SPR, the Swedish inpatient register
Obstetric embolism	Dichotomous (yes, no)	ICD-10 O88	SPR
Umbilical cord prolapse	Dichotomous (yes, no)	ICD-10 O69.0, P02.4	SPR
Vaginal delivery within 24 hours (VD24)	Dichotomous (yes, no)	As above within 24 hours after start of induction	SPR
Vaginal delivery within 48 hours (VD48)	Dichotomous (yes, no)	As above within 24 hours after start of induction	SPR
Stroke	Dichotomous (yes, no)	ICD-10 I61,X, I63.X	SPR, the Swedish inpatient register
Emergency or crash caesarean section	Dichotomous (yes, no)	ICD-10 O82.1	SPR
Indication for instrumental vaginal delivery or delivery by caesarean section		Foetal distress ICD-10 O.68.9, O36.3, Infection ICD-10 O75.3, O98.8, O98.9, Failure to progress ICD-10 O62.0-2, O62.8-9, Maternal distress during labour and delivery ICD-10 O75.0	SPR
Shoulder dystocia	Dichotomous (yes, no)	ICD-10 O66.0	SPR
Labor dystocia	Dichotomous (yes, no)	ICD-10 O.62.0-1, O62.8-9	SPR
Use of oxytocin	Dichotomous (yes, no)	DT036, DT037	SPR
Hypertonic, incoordinate and prolonged uterine contractions	Dichotomous (yes, no)	ICD-10 O62.4	SPR

Heavy vaginal bleeding before or during delivery	Dichotomous (yes, no)	ICD-10 O46, O67	SPR
Placental abruption	Dichotomous (yes, no)	ICD-10 O45	SPR
Number and reasons of visits and phone calls to the hospital in the outpatient group (balloon expulsion, planned visit after 24 h, PROM, pain, vaginal bleeding, contractions, impaired urination, foetal movements, delivery before reaching the hospital, other)			SPR, the Swedish inpatient register and regional registries as e.g. VEGA in the Wedstern Health care region
Need of additional induction method	Dichotomous (yes, no)	ICD-10 O61.X	SPR
Infection (before, during, after delivery	Dichotomous (yes, no)	O75.3, O85, O86, O91, O98, and see below	
Chorioamnionitis	Dichotomous (yes, no)	ICD-10 O41.1, V-nr 303	SPR, SNQ
Urinary tract infection	Dichotomous (yes, no)	ICD-10 O86.2	SPR
Endometritis	Dichotomous (yes, no)	ICD-10 O85.9, O86.1 O86.3, O86.8	SPR
Wound infection	Dichotomous (yes, no)	ICD-10 O86.0	SPR, the Swedish inpatient register
Sepsis	Dichotomous (yes, no)	ICD-10 A41	SPR, the Swedish inpatient register
Fever during delivery	Dichotomous (yes, no)	ICD-10 O75.2	SPR
Fever postpartum	Dichotomous (yes, no)	ICD-10 =86.4	SPR
Need and method of pain relief during delivery		ICD-10 ZXH50, ZXH40, ZXH10, SN999	SPR
Episiotomy	Dichotomous (yes, no)	Tick box (left, median, right) TMA00	SPR
Grade 3 or 4 perineal laceration	Dichotomous (yes, no)	Tick box sphincter, rectum ICD-10 O70.2-, O70.3, MBC33	SPR
Perineal laceration	Dichotomous (yes, no)	Tick box, ICD-10 O70	SPR
Amount of bleeding	Continuous (ml)		SPR

Postpartum bleeding >1000ml	Dichotomous (yes, no)	ICD-10 O72	SPR
Transfusion	Dichotomous (yes, no)	ICD-10 DR029, DR030, DR036-39	SPR
Breastfeeding at discharge from hospital	Dichotomous (yes, no)		SPR
Breastfeeding at follow-up visit to the midwife at 8-12 weeks postpartum	Dichotomous (yes, no)		SPR
Re-admission after delivery due to the mother's health	Dichotomous (yes, no)		SPR, the Swedish inpatient register
Experience of delivery	Continuous 1-10 Categorical • 0-3 • 4-7 • 8-10		SPR
Postnatal depression	Dichotomous (yes, no)	ICD-10 F53.X	SPR
Time variables			
Time from start of induction to 2nd stage of delivery	Continuous (hours, minutes)		SPR
Time from start of induction to delivery	Continuous (hours, minutes)		SPR
Duration of stay at the hospital	Continuous (hours, minutes)		SPR
Duration of stay at the hospital before delivery	Continuous (hours, minutes)		SPR
Duration of stay at the hospital after delivery	Continuous (hours, minutes)		SPR
Descriptive outcomes for the outpatient group only			
Delivery within 30 and 60 min from admission to hospital	Dichotomous (yes, no)		SPR
Caesarean section within 60 min from admission to hospital	Dichotomous (yes, no)		SPR
Arrival at the hospital by ambulance	Dichotomous (yes, no)		Ambureg
Delivery before reaching the hospital	Dichotomous (yes, no)		SPR

8.1.2.2. The woman's experience of outpatient versus inpatient induction

Women with low-risk induction experiences of induction in an outpatient setting and in a hospital setting will be measured by comparison of general self-efficacy (GSE), health-related quality of life

(HRQL, EQ-VAS, EQ-5D), Sense of Coherence (SOC-13), pain catastrophizing (PCS), anxiety and depression (HAD) before randomization.

The GSE, EQ-VAS, EQ-5D, SOC, PSC, HAD, EPDS, Childbirth experience 2 (CEQ2) and levels of breastfeeding (BES) will be measured 3 months after delivery.

Also, experience of the induction management will be evaluated by a questionnaire adapted from Bollapragada et al. including the following questions (41):

1 How do you think your labour went?

(1 = very easy…10 = very difficult)

2 Thinking back, how do you feel about the experience of the induction of labour? (1 = Extremely good…10 = Not at all good)

3. How painful do you think the induction of labour was?

(1 = Not at all painful…10 = Very painful)

4, How anxious were you during the induction of labor?

(1 = Not at all anxious…10 = Very anxious)

5. Would you have the same management of induction in your next pregnancy?

(1 = Definitely…10 = Definitely not)

6. Would you advise a friend to have the same management of induction of labor?

(1 = Definitely…10 = Definitely not)

In addition, the following open-ended free-text answer questions will be added:

1. What are your experiences of the childbirth?
2. What are your experiences about the management of the induction of labour?
3. Is there something else that you want to share with us in relation to your induction?

Questionnaires will be sent through a link via e-mail and/or SMS three months after delivery. The questionnaires will be eligible in Swedish. When validated translations of the instruments exist, these will be available even in other languages. Questions specifically developed for OPTION will be translated to other languages as well.

For all women, satisfaction with delivery will also be studied as registered in the SPR: After delivery all women delivering in Sweden are supposed to be asked how satisfied they are with their delivery rating from 1 (not satisfied) to 10 (satisfied). The proportion of women with experience rated as >7 and <4 will be compared between groups.

The GSE (42) consists of 10 items and each item is scored between 1 to 4, giving a possible score of 10 to 40. The EQ-VAS (42) is a vertical VAS 0–100 in which 0 is the lowest thinkable health state and 100 the optimal health state. The EQ-5D assesses dimensions of HRQL: mobility, self-care, activities of daily life, pain, levels of anxiety and depression. For each dimension, the woman describes three possible levels of problems (none, mild to moderate and severe). This descriptive system contains 243 combinations or index values for state of health. The total score range is from −0.43 to 1.0, in which -0.43 is the lowest health state, and 1, the highest. For a normal population, the average value is 0.8-0.9 (43). Sense of Coherence is measured by the 13-item Sense of Coherence Scale (SOC-13) and provides a total score for sense of coherence. Each item is scored on a Likert scale from 1 (low) to 7 (high), giving a possible range of 13-91 (44, 45).

The PCS was developed as a self-report measurement tool that provides a valid index of catastrophizing in clinical and non-clinical populations. The PCS is a 13-item self-report scale to measure thoughts and feelings related to pain (e.g. “when I am in pain, I worry all the time about whether the pain will end”). In the PCS, each item is rated on a 5-point scale: (in which 0 is not at all, and 4 constantly). A total score is calculated (range 0-65 points). The three subscales of magnification, rumination, and helplessness reveal different dimensions of the same underlying content. Anxiety and depression are measured by the Hospital Anxiety and Depression Scale (HADS) (42) and the Edinburgh Postnatal Depression Scale (EPDS) (43). The HAD is a 14-item scale for detection of anxiety and depression in people with physical health problems. Seven of the items relate to anxiety (HAD-A) and 7 items relate to depression (HAD-D). Each item on the questionnaire is scored from 0-3 and this means that a person can score between a total of 0 and 21 for either anxiety or depression. A cut-off point of 8/21 for anxiety or depression has been identified [50]. For anxiety this gave a specificity of 0.78, and a sensitivity of 0.9. For depression, this gave a specificity of 0.79, and a sensitivity of 0.83 (46). The Swedish version of the EPDS questionnaire consists of 10 items. Each item is scored from 1 to 4, giving a possible score of 10 through 40 (47). The CEQ 2 (34) consists of 20 items in four domains: Own capacity, perceived safety, professional support, and participation. Responses are scored using a 4-point Likert scale ranging from totally agree to totally disagree. Three items referring to labour pain (no pain) to (worst considerable pain), sense of security (no sence of security) to (total sence of security) and control (no sence of control) to (total sence of control) are assessed with a VAS (0-100 mm). Levels of breastfeeding self-efficacy will be measured through the Breastfeeding Self-Efficacy Scale short form (BES) (48). The BES scale consists of 14 items each scored on a likert scale between 1 to 5, giving a possible score between 14 and 70.

8.1.2.3. *The women's partner's experience of induction of labour in an outpatient versus inpatient setting*

Background characteristics as age, education level, number of children and number experiences of childbirths and induction of labour will be registered. The partners experiences of their pregnant partner's induction in an outpatient setting and in a hospital setting will be measured by comparison of general self-efficacy (GSE), health-related quality of life (HRQL, EQ-VAS, EQ-5D), Sense of Coherence (SOC-13), pain catastrophizing (PCS), anxiety and depression (HADS) before randomization as well as three months after delivery. EPDS and childbirth experience (Father for The First time questionnaire (FTFQ)) will be measured, analyzed and compared between groups three months after delivery (49). The FTFQ consists of 22 items rated on a four-point Likert scale assessing the father's/partner's experience of childbirth in four dimensions; worry, information, emotional support, and acceptance. Each dimension is evaluated separately using the mean score for the dimension as the result (range 1-4, where a lower score represents a better experience). No total score is calculated.

Also, experience of the induction management will be evaluated by a questionnaire adapted from Bollapragada et al, including the following questions (41):

1 How do you think your partners labour went?

(1 = very easy…10 = very difficult)

2 Thinking back, how do you feel about the experience of the induction of labour?

(1 = Extremely good…10 = Not at all good)

3. How painful do you think the induction of labour was for your partner?

(1 = Not at all painful…10 = Very painful)

4. How anxious were you during the induction of labour?

(1 = Not at all anxious…10 = Very anxious)

5. Would you like your partner to have the same management of induction in her next pregnancy?

(1 = Definitely…10 = Definitely not)

6. Would you advise a friend to have the same management of induction of labor?

(1 = Definitely…10 = Definitely not)

In addition, the following open-ended free-text answer questions will be added:

1. What are your experiences of the childbirth?
2. What are your experiences about the management of the induction of labour?

3. Is there something else that you want to share with us in relation to the induction of labour for your partner?

Further, the partners to participating women at Sahlgrenska university hospital will be asked to fill in free-text answers in a webb-based qualitative questionnaire adapted from Daniels et al, 2020 (27) three to six months after delivery

1. Can you describe how you felt when you became aware of your partner's pregnancy?
2. How involved were you during her pregnancy (e.g. did you attend antenatal classes, scans, midwife appointments, etc.). Please explain.'
3. What support (if any) did you receive from healthcare professionals for this pregnancy?
4. What support would you have liked to have received?
5. How did you feel when your partner went into labour? (Where were you when it happened, how did you hear about it, what did you do?)
6. What happened during the birth, to your partner and to you? Did you receive any antenatal preparation for your partner's birth and how did this preparation help you during your partner's labour?
7. Did you understand what was happening and can you explain why?
8. How in control/involved did you feel and why was this?
9. What support did you receive (if any) during the birth from healthcare professionals?
10. What support would you have liked to have received?
11. How did you feel after the birth?
12. What changes did you expect/not expect to happen after this birth?
13. To what extent has what you witnessed at the birth come back to your mind? Please describe.
14. Do you think this has affected your day to day life? If so, how?
15. Do you feel you have had an opportunity to talk to someone about it? If yes or no, please explain why.
16. Has a birth trauma affected your mood? If so, how
17. How do you think the birth trauma has affected the relationship you have with your partner?
18. What support did you receive (if any) after the birth from healthcare professionals?
19. What support would have liked to have received?
20. Is there anything else that you would like to tell us about your experience of the birth that the questions above did not address?

The questionnaires will be sent through a link via e-mail and/or SMS. When validated translations of the instruments exist, these will be available even in other languages. Questions specifically developed for OPTION will be translated to other languages as well.

8.1.2.4. Women's and their partners' experience of outpatient versus inpatient induction

Fifteen to -20 women and 15-20 partners will be interviewed 3-6 months after delivery. Informants will be selected to ensure a broad range of views and experiences of the phenomenon outpatient induction, e.g. age, parity and socio-economic background. For further description see below.

8.1.2.5. Care givers experience of outpatient induction

The phenomenon outpatient induction will be studied regarding the health care professionals' experience about six months after the introduction of outpatient induction at the Sahlgrenska University Hospital Gothenburg (and other sites that want to join the sub-study). Healthcare staff (n=20) will be chosen strategically according to age, gender, and profession (midwife, doctor), as well as working place (answering the phone, working at the induction unit, working at the delivery unit, working in postnatal care). Healthcare staff will be asked regarding their experience of working with low-risk women induced in an outpatient setting as compared to low-risk women induced at the hospital.

Data collection and data analysis for the interview part

The women, the partners and the health care professional respectively will receive both oral and written information and will be informed of the purpose and voluntary nature of the study. They will be assured that the data will be treated confidentially and that they are free to withdraw at any time. They in turn will give their written consent before answering the questionnaires or taking part in the interview.

Interviews will be conducted at the hospital or in the woman's/partner's/health care professional's home, depending on their preference. The informants will be interviewed separately. Face-to face interviews (50, 51) will be performed by a member of the research group or a research assistant/midwife. An open–ended question will be used "Please tell me of your experience of outpatient induction''. Follow-up questions such as "How did that feel" and "Can you please tell me more," will also be asked to deepen understanding. The interviewer will create an open climate to enable the informant to find the right words to express her/his experiences (52). Interviews will last approximately 1 h and will be audiotaped and transcribed verbatim. Data analysis will be conducted by either phenomenology with a lifeworld approach (53) or content analysis (50). NVivo8 software will be used to code and review categories (https://www.qsrinternational.com/).

8.1.2.6. Health economics

The following will be monitored: pregnancy, child, and maternal outcome including time from induction to delivery (hours, SPR, patient chart), time in the delivery unit (hours, SPR, patient chart), the number of calls to the midwife after start of induction (patient chart). Mode of delivery; spontaneous vaginal birth, instrumental vaginal birth, or caesarean section (SPR). Time from induction to active labour (SPR). Primary method of induction (SPR). If other method of induction is needed (SPR, patient chart). Duration of stay at hospital after delivery (SPR). Need of revisit postpartum (SPR, patient chart, the inpatient register). Readmission postpartum within the first month (SPR, patient chart, the inpatient register). Number and reasons of visits and phone calls to the hospital in the outpatient group (balloon expulsion, planned visit before and after 24 h, PROM, pain, vaginal bleeding, contractions, impaired urination, foetal movements, delivery before reaching the hospital, other) will be monitored at certain centres as these data are not available from the SPR, but from regional registers and/or patient charts.

8.1.2.7. Future deliveries

In a follow-up study 10 years after the initial study based on SPR data, number of future deliveries, mode of delivery, fear of childbirth, and patient satisfaction will be studied by linkage to the personal identification number.

8.2. Assessment of clinical safety

To evaluate if induction of labour in an outpatient setting is non-inferior to induction in hospital in a low-risk population regarding safety for the child as well as regarding efficacy, defined as proportion of women with vaginal delivery. Further pregnancy outcomes, the acceptability and experience of the woman, her partner and the staff, as well as future pregnancy outcome and health economic consequences will also be studied. Our hypothesis is that outpatient induction regardless of method (balloon catheter or oral misoprostol) is non-inferior to inpatient induction in low-risk women regarding the primary outcomes neonatal safety and efficacy.

Two primary outcomes have been defined: a composite outcome for neonatal morbidity and mortality* as well as an efficacy outcome defined as proportion of women with a vaginal delivery.

*Primary composite outcome: Stillbirth defined as intrauterine foetal death of a foetus that was alive at time of randomization, Neonatal death of a live born child that dies day 0-27, not including accidents or lethal malformation not known before randomization, Apgar score <4 at 5 minutes, pH <7.00 or base deficit >15 mmol/l in the umbilical artery, Hypoxic ischaemic encephalopathy I-III, intracranial haemorrhage, neonatal convulsions, therapeutic hypothermia, meconium aspiration syndrome, mechanical ventilation within first 72 hours, neonatal pneumonia, neonatal sepsis, nicus admission >48 hours duration.

Three interim-controls regarding safety and SAE will take place – please see section 8.3

9. Handling of Adverse Events

Adverse events including Adverse Drug event and Adverse device effect and SAE, SADE, SUSAR, USADE:

All AE will not be reported in this study since this is not aim of the study, since both Angusta® as well as the use of Foley catheter is well known in clinical practice and Angusta® is approved for home induction in Denmark. However, the following will be reported as AE in conjunction with events which are totally unexpected:

Angusta® - hyperstimulation, wrong intake (for example vaginal instead of oral, too many tablets at the same time, intake closer than 2 hours apart).

Balloon catheter - come apart, misplaced, urinary retention, the baby changes from head to breech.

Severe adverse events (SAE) and Suspected unexpected serious adverse reactions (SUSARs) will be registered and followed at all participating hospitals and reported to the DSMB and the chair of DSMB will report to the Medical Products Agency (MPA) within two calendar days for life-threating events and within seven days for others. When assessing SAEs the causal nature and time from the intervention to the SAE need to be considered by the responsible investigator at the centre. The members of the steering group will not be informed on SAEs to maintain the blinding until the study is finished.
All participating study sites have to report the following severe adverse events (SAE)
For the child:

- Intrauterine death or neonatal death up to 27 days after delivery
- Admission to neonatal intensive care unit for more than 48 hours before discharge home
- Umbilical cord prolapse

For the woman:

- Maternal death up to 42 days after delivery
- Mother admitted to intensive care unit
- Uterine rupture / hysterectomy in connection to the delivery
- Delivery outside the hospital or within 15 minutes from admission
- Woman re-admitted to the hospital due to serious events such as pulmonary embolism and sepsis after delivery within 42 days

Serious adverse device effects (SADEs) are any adverse device effects that resulted in any of the consequences characteristic of an SAE. In the case of the balloon catheter, this includes device deficiencies that might have led to a serious adverse event if a suitable action had not been taken, intervention had not been made or circumstances had been less fortunate. These are handled under the SAE reporting system.

Suspected unexpected serious adverse reactions (SUSARs) are reactions/events that are unexpected, serious, and suspected to be caused by the treatment, i.e. adverse events that are not included in the summary of product characteristics. These are handled under the SAE reporting system.

Since this study is an investigator-initiated non-commercial study where the principal investigator lacks the ability to report directly into the European database of side effects (EudraVigilance) We therefore ask the Competent Authority for help. SUSAR is reported via CIOMS-form that will be sent to registrator@mpa.se.

SAEs for the Foley catheter will be reported at:
https://e-service.lakemedelsverket.se/formservice/formDownload?serviceName=file_upload_lakemedelsverket&scriptcomponent.cmtagname=trex-lakemedelsverket-file_upload-cfd&service_name=file_upload

Unanticipated serious adverse device effects (USADEs) are SADEs which by their nature, incidence, severity or outcome have not been identified in the current version of the risk analysis report and as such are unanticipated.

All SAEs, SADEs, USADEs should be followed until they are resolved or the DSMB assesses that they are chronic or stable or the patient's participation in the study ends.

The study will also be monitored by an independent monitor before the study begins, during the study conduct, and after the study has been completed, so as to ensure that the study is carried out according to the protocol and that data is collected, documented, and reported according to ICH-GCP and applicable ethical and regulatory requirements. Monitoring is performed as per the study's monitoring plan and is intended to ensure that the subject's rights, safety, and well-being are met as well as data in the eCRF are complete, correct, and consistent with the source data.

9.1. Definitions

9.1.1. Adverse Event (AE)

Adverse event (AE): Any untoward medical occurrence in a clinical investigation subject administered a medicinal product or medical technical product and, which does not necessarily have a causal relationship with the treatment, can be an unfavourable and unintended sign (including an abnormal laboratory discovery), symptom or disease temporally associated with the use of the medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The following will be reported as AE in conjunction with events which are totally unexpected:

Angusta® - hyperstimulation, wrong intake (for example vaginal instead of oral, too many tablets at the same time, intake closer than 2 hours apart)

Balloon catheter - come apart, misplaced, urinary retention, the baby changes from head to breech will be reported to the DSMB.

9.1.2. Adverse Drug Reaction (ADR) and Adverse Device effect

In the use of a well-known medicinal product (Angusta®) and a well-known medical technical product such as Foley /cook catheter in a new context, all noxious and unintended responses should be considered adverse drug reaction (ADR) or Adverse Device Effect (ADE). The phrase "response"

means that the causal relationship between the medical product and medical technical product and an adverse event is at least a reasonable possibility, that is the relationship cannot be ruled out.

9.1.3. Serious Adverse Event (SAE)

The standard SAE are not applicable for the design of this study. Admission to the hospital is what happens for all women in the inpatient group immediately and is expected and wanted for all study participants in the outpatient group within 1 to 3 days from inclusion. As most of the women will enter the active phase of delivery after the cervical ripening phase, most women in this study will become subject to other treatment such as e.g. pain relief such as epidural, oxytocin infusion or antibiotic treatment in case of PROM.

Therefore, the participating study sites are asked to report the following severe adverse events (SAE)
For the child:

- Intrauterine death or neonatal death up to 27 days after delivery
- Admission to neonatal intensive care unit for more than 48 hours before discharge home
- Umbilical cord prolapse

For the woman:

- Maternal death up to 42 days after delivery
- Mother admitted to intensive care unit
- Uterine rupture / hysterectomy in connection to the delivery
- Delivery outside the hospital or within 15 minutes from admission
- Woman re-admitted to the hospital due to serious events such as pulmonary embolism and sepsis after delivery within 42 days

Serious adverse device effects (SADEs) are any adverse device effects that resulted in any of the consequences characteristic of an SAE. In the case of the balloon catheter, this includes device deficiencies that might have led to a serious adverse event if a suitable action had not been taken, intervention had not been made or circumstances had been less fortunate. These are handled under the SAE reporting system.

Medical and scientific assessment will be made to determine if an event is “serious” and whether it would prompt reporting in other situations, for example important medical events that may not be directly life-threatening or result in death or hospitalization but may compromise the study subject or may require intervention to prevent one of the other results set forth in the definitions above. These should also normally be considered as SAEs.

9.1.4. Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected unexpected serious adverse reactions (SUSARs) are reactions/events that are unexpected, serious, and suspected to be caused by the treatment, i.e. adverse events that are not included in the Investigator’s Brochure (IB) or SPC. These are handled under the SAE reporting system.

9.2. Assessment of adverse events

9.2.1. Assessment of causal relationship

The investigator is responsible for determining whether there is a causal relationship between the AE/SAE and use of the investigational product.

Those AEs which are suspected of having a relationship to the investigational product will be followed up until the study subject has recovered or is well taken care of and on their way to good recovery, hence until discharge from hospital of mother and child (see also section 0,

).

All AE as stated in 8.1.1 experienced by the subjects receiving Angusta®, will be categorized either as likely related, possibly related, or not related, in accordance with the definitions below:

Likely related: Clinical event, including abnormal results from laboratory analyses, occurring within a reasonable time after administration of the intervention/investigational product. It is unlikely that the event can be attributed to underlying disease or other medications, but is most likely caused by the investigational product and its emergence is reasonable in relationship with use of the investigational product.

Possibly related: Clinical event, including abnormal results from laboratory analyses, occurring within a reasonable time after administration of the intervention/investigational product. The event could be explained by the investigational product and its emergence is reasonable in relationship with use of the investigational product, but there is insufficient information to determine the relationship. The event could be explained by an underlying disease or other medications.

Not related: Clinical event, including abnormal results from laboratory analyses, that is not reasonably related to the use of the intervention/investigational product. The event is unlikely related to the intervention/investigational product and can be explained by other medications or underlying disease.

All AE as stated in 8.1.1 experienced by subjects induced by the method balloon catheter, will be categorized either as not related, unlikely, possible, probable, causal relationship.

Not related:
relationship to the device or procedures can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the investigational device or the procedures;
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;

- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
- harms to the subject are not clearly due to use error;
- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Unlikely:
the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

Possible: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probable: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
o the investigational device or procedures are applied to;
o the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

9.2.2. Assessment of severity

Each adverse event shall be classified by an investigator as mild, moderate or severe.

Mild: The adverse event is relatively tolerable and transient in nature but does not affect the study subject's normal life.

Moderate: The adverse event causes deterioration of function but does not affect health. The event can be sufficiently unpleasant and interferes with normal activities but does not completely obstruct them.

Severe: The adverse event causes deterioration of function or work ability or poses a health risk to the study subject.

Assessment of severity is generally made by the reporting investigator.

9.3. Reporting and registration of adverse events

At each study visit, adverse events (AE) are registered from start of treatment with the investigational product, up to and including discharge from hospital of mother and child. SAE such as neonatal death up to 28 days and maternal death until 42 days after delivery will be followed by registers.

All AE as stated above in section 8.1.1 will be registered in the eCRF regardless of whether they are related to the investigational product or not. Assessment of causal relationship, severity, and whether the AE is considered to be an SAE or not will be done by the investigator directly in CRF/on study-specific worksheet. At minimum, for each AE/SAE, a description of the event is recorded (diagnosis/symptom if diagnosis is missing), start and stop dates, causal relationship, severity, if the AE is considered to be an SAE or not, measures and outcome.

The following symptoms are clearly related to the process and the expected course of condition and therefore will not be reported as AE:

- Expected adverse events based on knowledge of a delivery and expected clinical course.
- Hospitalization since this is the expected course of the start of the delivery. However, a mother admitted to intensive care unit or re-admitted to the hospital due to serious events such as pulmonary embolism and sepsis after delivery within 42 days will be included

All AE shall be registered at the latest at delivery and notified the responsible clinical investigator at the study site.

9.3.1. Reporting of serious adverse events (SAE)

Severe adverse events (SAE) and Suspected unexpected serious adverse reactions (SUSARs) will be registered and followed at all participating hospitals and reported on a special SAE form within 24 hours of the investigator being informed of the SAE to the DSMB. The chair of DSMB will report to the Medical Products Agency (MPA) within two calendar days for all reportable events which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it and within seven calendar days for other SAEs. This is only for the events experienced by subjects induced by balloon catheter.

The chair of DSMB will report SUSARs (experienced by subjects induced by Angusta®) to the Medical Products Agency (MPA). For fatal and life-threatening SUSARs, this will be done no later than 7 calendar days after the DSMB is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

When assessing SAEs the causal nature and time from the intervention to the SAE need to be considered by the responsible investigator at the centre. The members of the steering group will not be informed on SAEs to maintain the blinding until the study is finished.
Follow-up information describing the outcome and handling of the SAE is reported as soon as this information is available. The original should be kept in the Investigator Site File.
The DSMB will assess the severity and the clinical relevance.
The Committee will be composed of 4 members (inclusive of the DSMB Chair). The DSMB includes experts in or representatives of the appropriate fields, such as obstetrics, paediatrics and statistics.
Members of the DSMB are:

1. Lars Ladfors, senior consultant and associate professor in obstetrics at Sahlgrenska University Hospital and Chair of DSMB
2. Göran Wennergren, Professor Emeritus in Paediatrics at Sahlgrenska University Hospital and co-chair
3. Mia Ahlberg, PhD, Head of midwifery science and development at Karolinska University Hospital
4. Fredrik Granath, Associate Professor at Karolinska University Hospital and biostatistician

The Chair is responsible for convening the DSMB. A meeting will take place at the interims-analysis (1000, 3500 and 6000) as well as at the finalization of the study. Additional meetings will also take place at extra-ordinary events related to a SAE. The chair will then convene for an extra session, hence the number of sessions during the study period for the DSMB depends on the number of SAEs and what kind of SAEs that happens. The SAEs will be presented to the DSMB blinded initially, but the DSMB will always have the right to know upon request which study arm the SAE has happened in.

9.3.2. Reporting of Suspected Unexpected Serious Adverse Reactions (SUSAR)

See section 8.3.1. Those SAE which are assessed by DSMB to be SUSAR are reported to the Swedish Medical agency since this is a non-commercial driven study where the investigators lack ability to report directly into the EudraVigilance database.
SUSARs should, if possible, be reported unblinded, that is, should state to which investigational product the subject had a reaction.
SUSAR that are fatal or life-threatening are reported as soon as possible and no later than 7 days after the incident has become known to the DSMB. Relevant follow-up information is sent thereafter within an additional 8 days. Other SUSAR are reported as soon as possible and no later than 15 days after they have come to the knowledge of the DSMB.
Multi-centre studies: Information about SUSAR occurring during the study is compiled by the DSMB and sent out to the principal investigator at all participating centres.

9.4. Independent Data Monitoring Committee

See section 8.3.1.
The study will be monitored by a data safety monitoring board (DSMB). The primary objective of the DSMB is to monitor the safety of the intervention and the validity and integrity of the data from the clinical study. As the coordinating principal investigator and sponsor should remain blinded throughout the study, the responsibility for collecting, follow-up, classification and reporting of AE, SAE and SUSAR to Swedish Medical Products Agency has been delegated to the DSMB. The DSMB will however, inform the sponsor in case they judge that reported AE, SAE or SUSAR affect the safety of the study participants.

Additionally, the DSMB will make recommendations to the sponsor regarding the continuation (if a too slow pace of recruitment is noticed that could affect the safety of the study), modification, or termination of any or all arms of the study.

Three interim analyses will be performed; after the first 1000, 3500, and 6000 women have given birth. Regarding “modification” the DSMB will have the mandate to exclude one of the induction methods (balloon catheter or oral prostaglandin) from continuation in the study if adverse events

can be linked explicitly to one induction method. The study can then proceed with the other method. The DSMB might even exclude certain patient groups from continuation. Patient groups that will be studied in sub analysis during the interim analyses are primiparous vs multiparous women and women induced due to premature rupture of the membranes (PROM) vs other reasons for induction.

9.5. Annual Safety Report (Development Safety Update Report, DSUR)

As long as the study is in process in Sweden, the sponsor is obliged to submit an annual safety report to the Swedish Medical Products Agency. It defines for which time period the report applies and a list of all SAE that have occurred as well as possibly SUSAR. A summary assessment of the safety situation for the study subjects and a risk/benefit evaluation for the study must also be described. Note that information to EPM about SUSAR and annual safety reporting are requirements according to LVFS but not EPM. As the sponsor should remain blinded throughout the study period, the sponsor commissions this task to the DSMB.

9.6. Procedures in case of emergencies, overdose or pregnancy

N/A

9.7. Reference Safety Information

Uterine hyperstimulation with fetal heart rate changes has been associated with Angusta®. The risk for this is lower for balloon catheter, but the rate of failed induction is higher, hence more c-sections. SPC for Angusta® is available and IB is available for the Foley Catheter.

10. Statistics

10.1. Analysis population

The primary analysis and the first secondary analysis are non-inferiority analyses and hence analysed according to both ITT population and Per Protocol population. The only women who will be excluded from the Per Protocol analysis will be women who do not consent to go home after randomization. Women who e.g. experience rupture of the membranes after randomization but before leaving the hospital or women who might experience contractions or bleeding on their way home will be analysed in the outpatient group even in the Per Protocol analyses as admission of these women is part of the protocol.
An “as treated” analysis will be performed analysing women randomized to the outpatient group, but remaining inpatient due to not consenting to the outpatient setting in the inpatient group. No women in the inpatient group have the possibility to cross over to the outpatient group.

10.2. Statistical analyses

10.2.1. Statistical methods

Two primary non-inferiority outcomes have been defined. One composite safety complication outcome which will be analysed with a two-sided 95.7% confidence interval (CI) and one efficacy vaginal delivery (VG) outcome which will be analysed with a two-sided 99.3% CI in order to have a total Type I error <0.05. If non-inferiority is confirmed for one of them but not for the other, the other will be reanalysed according to decision rules of the Holms Test with 95% CI.

All the main analyses will be performed on the ITT population and complementary analyses will be performed on the PP population.
For comparison between the two randomized groups, Fisher's exact test will be used for dichotomous variables, Fisher's non-parametric permutation test for continuous variables, Mantel-Haenszel chi-square test for ordered categorical variables, and Pearson's chi-square test for non-ordered categorical variables.
For all comparison between the two groups, regarding dichotomous and continuous variables, mean differences with 95% CI will be calculated.
All the main analyses will be unadjusted. If significant and clinically relevant baseline confounders are found, complementary analyses will be performed adjusted for these baseline variables. For primary outcome variable and other dichotomous outcome variables multivariable binary regression will be used for the adjustment. For continuous variables ANCOVA will be used for the adjustment.
For dichotomous variables risk difference with 95% confidence interval (CI) and risk ratio with 95% CI will be calculated between the two groups and exact 95% confidence intervals for the estimated proportions. The distribution of continuous variables as well as change in continuous variables will be given as mean, SD, median, minimum, maximum and 1st and 3rd quartiles. Categorical variables will be given as number and percentages. All presentation of the results will be given by treatment group. All significance tests will be two-sided and conducted at the 5% significance level.

1. Primary safety and efficacy analyses.

First primary safety analysis is the non-inferiority comparison of the primary composite perinatal outcome in the outpatient induction group compared to the hospital induction group on the ITT population. A two-sided 95.7% CI, with Nurminien and Miettinen's method, for the difference in percentage in primary composite perinatal outcome between outpatient and inpatient group will be constructed. If the upper limit of this 95.7% CI is less than 1.5%, then non-inferiority will be confirmed.
First primary efficacy analysis is the non-inferiority comparison of proportion of women with a vaginal delivery in the outpatient induction group compared to the hospital induction group on the ITT population. A two-sided 99.3% CI, with Nurminien and Miettinen's method, for the difference in percentage in vaginal delivery between outpatient and inpatient group will be constructed. If the upper limit of this 99.3% CI is less than 1.5% then non-inferiority will be confirmed. If non-inferiority is confirmed for one of them but not for the other, the other will be reanalysed according to decision rules of the Holms Test with 95% CI.
If any of these CI's does not contain 0 superiority is confirmed.

Exactly the same analyses will also be performed on the PP population.
Risk ratio (RR) and exact 95% CI will be calculated between the two groups for the estimated proportions of primary outcomes per groups. If significant and clinically relevant differences are found between the two groups regarding baseline variables a complementary multivariable generalized estimating regression model with distribution binomial and link function log will be used to estimate RR adjusted for these baseline variables. A complementary primary analysis will also be performed with centre as random effect and with interaction term centre*randomized group.

Primary efficacy analyses will also be performed by region (defined in 6.9) and by centre. Centres with less than 50 patients will be collapsed to one group “Small centres”.

2. Secondary efficacy analysis, time related analyses and analyses of experiences.
The same non-inferiority analyses as in the primary efficacy analysis of vaginal delivery will be analysed with 95% CI with the same non-inferiority margin within the balloon catheter group and in the oral misoprostol group.
Secondary efficacy analyses will be the analyses between the two randomized groups regarding all variables listed in under “Primary and secondary health outcomes” (secondary neonatal and maternal outcome variables) and women’s experience above with the statistical methods given in section 6.2 (General statistical methodology) above on the ITT population. Complementary secondary efficacy analyses will be the analyses of primary composite perinatal outcome and all secondary efficacy variables between the two randomized groups on the PP population. All the secondary efficacy analyses will be two-sided and conducted at the 5% significance level.

3. Exploratory Efficacy Analyses, Time related analyses and analyses of experiences.
Variables listed above under “Primary and secondary health outcomes” as well as variables regarding the woman’s and partner’s experience will be analysed between the two randomized groups with the statistical methods given in section 6.2 (General statistical methodology) on the ITT population and on the PP population.

4. Analysis of demographics and baseline characteristics
All demographics and baseline characteristics will be described and analysed between the two randomized groups according to the methods given in section 6.2 (General statistical methodology) above.

5. Subgroup analysis:
Subgroup analysis are planned for all outcomes for
1) primiparous versus parous women
2) depending on the initial method of induction (balloon versus prostaglandin)
3) depending on initial Bishop score in women without PROM (<3 versus $\geq$ 3)
4) depending on indication for induction (PROM versus other than PROM)
5) reported time to hospital < 30 minutes and >= 30 minutes.

6. Exploratory Analyses of interactions to treatment effect
Analysis of interaction will be made for variables potentially affecting primary efficacy analysis (to be defined in the statistical analysis plan (SAP). For baseline variables with interaction p-value < 0.10 subgroups analyses will follow.

7. Statistical Analysis Plan (SAP)
A statistical analysis plan (SAP) that describes all detailed statistical analyses will be written prior to any analysis.

8. Health economics

A cost-effectiveness analysis will be performed comparing induction in an outpatient to induction in a hospital-based setting. The primary measure of effectiveness will be comparable to the composite outcome defined as primary outcome in this study (54). If non-inferiority is established, a simpler cost-minimization analysis will be conducted, i.e. only analysing differences in economic costs (and not in relation to the clinical outcomes). All analyses will focus on differences in means between costs and between clinical outcomes. Since cost data is typically non-normal, sampling uncertainty on differences in costs and cost-effectiveness will be assessed by non-parametric bootstrapping (54). Applying a simulation model, cost effectiveness for a longer time horizon will be assessed by extrapolation. To do so, associations between neonatal and maternal morbidity and health outcomes later in life will be estimated based on available epidemiologic literature (55).

10.2.2. Drop-outs

Se section 9.1.

10.3. Adjustment of significance and confidence interval

Se section 9.2.

10.4. Sample size calculations

The study aims to establish non-inferiority of outpatient induction regarding safety for the child in the whole group, as well as efficacy (proportion of vaginal deliveries) in the whole group as well as in the subgroups of women induced with either balloon catheter or prostaglandin. We are not able to predict the proportion of women who will be induced by balloon or prostaglandins, which is why two separate power calculations have been performed.

10.4.1. Safety

According to data from the SPR 2014-2018 the incidence of the primary composite safety outcome in the group of women aged 18-45, BMI ≤35 with simplex pregnancy, gestational length 37+0 to 41+6, no previous caesarean delivery, no IUFD, and no diagnosis of hypertension/preeclampsia (O10, O11, O13, O14, O15), gestational diabetes with medical treatment or diabetes type 1 or type 2 diagnoses (O24.0, O24.1, O24.3) was 2.3%. Based on incidence data from INDEX (3) and SWEPIS (2), where a similar composite endpoint was used, an assumption was made regarding an incidence of the safety outcome of 2.8% in the outpatient arm.

The primary, non-inferiority hypothesis will be tested by constructing a two-sided 95% confidence interval (CI) for the difference in percentage of primary outcome between outpatient and inpatient induction. Given 2.8% in outpatients and 2.3% in inpatients for the primary composite outcome, we need to include 4223 women in each arm in order to achieve a probability of ≥0.80 that the upper limit of a two-sided 95.7% CI for the difference in primary outcome between outpatient and inpatient induction will be less than the non-inferiority margin 1.5%. With a 5% drop-out rate in each group 4445 women need to be *randomized* to each arm and hence in total at least 8891 women.

10.4.2. Efficacy

The vaginal delivery rate was 88% in the group of eligible women (SPR, 2014-2018). Assuming a vaginal delivery rate of 90% in the outpatient arm, calculating with 80% power, 99.3% CI, a non-inferiority margin of 0.015 and a 5% drop-out rate, 2119 women need to be randomized to each arm induced with either balloon catheter or prostaglandin.

Thus, the study will proceed until 2119 women are randomized in each arm and induced with balloon catheter or oral misoprostol, respectively. This is in order to have power to study the efficacy outcome (vaginal delivery) in the subgroups of women induced with balloon catheter as well as prostaglandin alone.

10.4.3. Feasibility

In Sweden, 19% of all deliveries were induced in 2018 (SPR). Since 22% of all pregnant women/year reach gestational week 41+0, we estimate that the total proportion of women who will require induction will reach 30% after a policy change to general induction in week 41+0. According to the literature and data from hospitals in Finland and Denmark ((10), personal communication), about 42-75% of all induction are classified as low-risk and suitable for outpatient induction. Based on these data, we estimate that 17,000 women in Sweden would be eligible for this study each year. The hospitals that have preliminarily signed up for contribution to this study handle approximately 70% of all deliveries in Sweden/year (approximately 78,000 deliveries). As inductions need to be performed every day of the week all year, inclusion may proceed even during holiday time. With a 30% inclusion rate (based on data from the Pregnancy Panel that 35% of pregnant women would prefer outpatient induction (www.pregdem.se)), recruitment could be achieved within 2.5 years.

10.4.4. The woman's experience of induction and delivery

Sample size for women's experience has been calculated for the total scoring of the CEQ. According to data from the SWEPIS early induction group, mean total CEQ in this group was 3.31 with a standard deviation of 0.52. Effect sizes regarding childbirth experiences between groups are thought to de: 0.2-0.5 = Small, 0.5-0.8 = Moderate, > 0.8 = Large (34).

Assuming a mean CEQ of 3.31 in the inpatient and of 3.21 in the outpatient arm, calculating with 80% power, 95.0% CI, a non-inferiority margin of 0.2 and a 5% drop-out rate, 530 women need to be randomized to each arm induced with either balloon catheter or prostaglandin. This would mean that 25% of all women randomized need to fill out the CEQ which is deemed feasible.

10.4.5. Health economics

Based on a hypothesized difference in mean costs (SEK 3,000) between the treatment groups and one standard deviation (SEK 20,000) from the SWEPIS study (1), sample size calculations (Alpha=0.05, Power=0.8) indicate that 750 women need to be included in each treatment arm for the economic analysis.

10.5. Interim analysis

Since this is a non-inferiority study only safety and not efficacy will be taken into account. Three interim analyses will be performed; after the first 1000, 3500, and 6000 women have given birth. The SAE and SUSAR will be reported to the DSMB directly keeping the sponsor blind of study arm that the SAE/SUSAR belongs to. The DSMB will have the mandate to exclude one of the induction methods (balloon catheter or oral prostaglandin) from continuation in the study if adverse events can be linked explicitly to one induction method. The study can then proceed with the other method. The DSMB might even exclude certain patient groups from continuation. Patient groups that will be studied in sub analysis during the interim analyses are primiparous vs multiparous women and women induced due to premature rupture of the membranes (PROM) vs other reasons for induction.

11. Quality Control and Quality Assurance

The study will also be monitored by an independent monitor before the study begins, during the study conduct, and after the study has been completed, so as to ensure that the study is carried out according to the protocol and that data is collected, documented, and reported according to ICH-GCP and applicable ethical and regulatory requirements. Monitoring is performed as per the study's monitoring plan and is intended to ensure that the subject's rights, safety, and well-being are met as well as data in the eCRF are complete, correct, and consistent with the source data. The monitor's qualifications will be documented.

11.1. Quality Assurance and Sponsor oversight

The monitor will have regular contacts with the clinic to verify informed consents of participating subjects, to confirm that facilities remain acceptable, that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRFs and to verify inclusion/exclusion criteria.
The investigator should ensure that all persons assisting with the trial are adequately informed and trained about the protocol, the investigational products(s) and their trial related duties and factions. The monitor will check that training has been performed and that this is documented. The monitor will also ensure source data verification (comparison of the data in the CRF with the medical records and other source data). The monitor must have direct access to source data. The extent of monitoring is defined in a monitoring plan.

11.2. Monitoring

The study will be monitored by an independent monitor before the study begins, during the study conduct (will check the first 3 patients included on each site within two weeks after starting the study at that site), after 500 included patients and after the study has been completed, so as to ensure that the study is carried out according to the protocol and that data is collected, documented, and reported according to ICH-GCP and applicable ethical and regulatory requirements. Monitoring is

performed as per the study's monitoring plan and is intended to ensure that the subject's rights, safety, and well-being are met as well as data in the CRF are complete, correct, and consistent with the source data. The monitor will also take part in the interim controls.

11.3. Source data

Data is registered directly in the eCRF. The eCRF is contained within the Pregnancy Register, a certified National Quality Registry initiated by the Swedish Healthcare. The register collect and process information all the way from early pregnancy to a few months after birth. In the eCRF, data such as parity, indication for induction, method for induction, reason for inclusion, number and time for tablet intake will be quality controlled by research staff. The pregnancy register itself is a validated register. The information in the Registry is protected by Swedish law and may be used only for the development of better health care and research. Through the use of anonymous personal data, encryption, and secure logon, they ensure that no unauthorized person can access the information.

Date and time for induction as well as tick boxes for "main" and "secondary indication for induction" with the following choices will be added to the eCRF as indication for induction is not reliably available from the SPR:

- late term ≥41+0 to 41+6 weeks
- dietary treated gestational diabetes without macrosomia
- stable hypertension (gestational or essential)
- large for gestational age/macrosomia without diabetes diagnosis
- prolonged latent phase, number of whole hours
- maternal age
- mild intrahepatic cholestasis with serum bile acids <40 µmol/L
- pregnancy-related pelvic girdle pain
- premature rupture of membranes (for prostaglandin method only)
- induction of labor without medical reason (psychosocial)
- other, specify (free text)

Time to hospital in minutes according to the woman's estimation and whether the woman will stay in a patient hotel (defined as no interventions or surveillance available) will be recorded in the eCRF.

Women who have given consent to participation, but are excluded before randomization due to resulting exclusion criteria after examination, will be registered in the eCRF and the reason for exclusion will be marked in tick boxes:

- SGA according to ultrasound examination
- Oligohydramniosis according to ultrasound examination
- Polyhydramniosis with AFI >300 mm
- Foetal malformation affecting delivery or immediate care for the neonate
- Low-lying placenta according to ultrasound examination
- Start of contractions
- PROM (in case PROM was not indication for induction)
- Severe bleeding (at the discretion of the physician)
- Pain – more than expected discomfort (at the discretion of the physician)

- Fever
- CTG not classified as normal
- Withdrawal
- Other, specify (free text)

Further time for intake of Angusta® will be registered in the eCRF.

11.4. Deviations or serious breaches

Serious breaches and deviations from the study protocol, GCP and other regulations that significantly and directly affects, or with high likelihood could affect, the subjects in Sweden or the scientific value of the study, shall be immediately reported (from knowledge) to the Swedish Medical Products Agency (MPA). It is the sponsor's responsibility to judge the consequences of deviations that have occurred, and thus also to decide whether the MPA should be informed.

Minor deviations that do not affect subjects' integrity or safety, nor significantly affect the study's scientific value, are documented in the study documentation of the principal investigator and the sponsor.

11.5. Audits and inspections

Authorized representatives for the sponsor and Competent Authorities (CA) may carry out audits or inspections at the study site, including source data verification. The investigator must ensure that all source documents are available for audits and inspections. The purpose of an audit or inspection is to systematically and independently review all study-related activities and documents, so as to determine whether these activities were performed, registered, analyzed and reported correctly according to protocol, Good Clinical Practice (GCP) and applicable regulations.

12. Ethics

12.1. Compliance to the protocol, GCP and regulations

The study will be performed in accordance with the study protocol, ICH-GCP E6 (R2), the latest version of the Declaration of Helsinki and applicable regulatory requirements. This is to ensure the safety and integrity of the study subjects as well as the quality of the data collected.

12.2. Ethical review of the study

The final study protocol, including the final versions of the informed consent form and other information provided to subjects *has been approved* by the Swedish Ethical Review Authority (Etikprövningsmyndigheten, EPM) Dnr 2020-02675 (200703). The EPM must be informed of any changes in the study protocol in accordance with applicable requirements.

12.3. Procedure for obtaining informed consent

The principal investigator at each site shall ensure that the subject is given full and adequate oral and written information about the study, its purpose, any risks and benefits as well as inclusion and exclusion criteria. Subjects must also be informed that they are free to discontinue their participation in the study at any time without having to provide a reason. Subjects should be given the opportunity to ask questions and be allowed time to consider the provided information. If the person chooses to

participate, both the subject and the investigator shall sign the informed consent form. The subject's signed and dated informed consent must be obtained before performing any study-specific activity in the study. Each subject who participated in the study will be identified by a study ID given when filling in the eRCF. The subject agrees that monitors and inspectors may have access to their medical records. If new information is added to the study, the subject has the right to reconsider whether he/she will continue their participation.

12.4. Data protection

If any part of the data is handled by any other organization, inside or outside the EU, appropriate agreements and/or other documentation will be established, to ensure that the data processing is performed in accordance with the provisions of the General Data Protection Regulation (GDPR) and other relevant legislation, before any data transfer takes place.

The content of the informed consent form complies with relevant integrity and data protection legislation. In the subject information and the informed consent form, the subject will be given complete information about how collection, use and publication of their study data will take place. The subject information and the informed consent form will explain how study data are stored to maintain confidentiality in accordance with national data legislation.

The Swedish Pregnancy Register (SPR) will be used for randomization and data registration through an attached electronic Case Report Form (eCRF) specifically developed for the study by MedSciNet AB, Stockholm, Sweden. An OPTION database will be established via MedSciNet, the platform for the SPR and SNQ. MedSciNet has experience setting up eCRF and databases like this from e.g. the SWEPIS (1) and CDC4G study (35). Data from the different registries, the eCRF and the questionnaires will be linked through the personal identification number and afterwards replaced by a studyID. The code key will be kept separated with only PI and co-investigator having access and researchers will only have access to pseudonymized data. Data and the data key will be kept for 20 years to guarantee long-time follow-up of the mothers and children.

Data regarding pregnancy and delivery will be obtained through the SPR (36). If a child is admitted to the neonatal intensive care unit (NICU), data regarding child health will be obtained from SNQ (37). Postpartum complications will be collected by linkage between registers from the National Board of Health and Welfare (National Patient Register, National Cause of Death Register and Prescribed Drug Register). Data regarding maternal or perinatal death will be collected through Statistics Sweden (SCB) and the National Cause of Death Register as some deaths after discharge from the hospital otherwise would go unnoticed for the study group. Deaths not related to pregnancy, e.g. traffic accidents will not be taken into account. Data regarding if a woman came to the hospital by ambulance will be extracted from the Swedish Ambulance Register (38). Data on family income and education will be collected from SCB (Register of Total Population, Education Register, and Income Register).

Certain data cannot be obtained through the quality registries and will be obtained through medical records and entered into the eCRF. Data on women's and their partners' experience of induction will be obtained through self-administered questionnaires. Health economic data such as days in hospital will be collected from SPR and medical records and entered into the eCRF. Interview data will be recorded, transcribed and added to the eCRF. Data in the eCRF will be saved for at least 10 years or as per relevant regulations.

Within publications no single person will be able to be identified.

The informed consent form will also explain that for verification of the data, authorized representatives of the sponsor, as well as relevant authority, may require access to parts of medical records or study records that are relevant to the study, including the subject's medical history.

12.5. Insurances

The study subjects are covered by the Swedish Patient Injury Act and the Pharmaceutical Insurance (http://lff.se/).

13. Substantial changes to the study

Substantial changes to the signed study protocol are only possible through approved protocol amendments and by agreement from all responsible persons. Information on non-substantial changes should be clearly noted in the amended protocol.

In the event that substantial changes to the protocol (e.g., changing of the main objective, primary or secondary variables, method to measure the primary variable, changing of the investigational product or dosage) will be made during the course of the study, approval from the Swedish Ethical Review Authority (Etikprövningsmyndigheten, EPM) as well as the Swedish Medical Products Agency (Läkemedelsverket) shall be obtained before any changes are implemented. A change that concerns a new site, new investigator or a new study patient information sheet shall only be approved by EPM.

Non-substantial changes will be recorded and later entered in documentation that is submitted, for example in any subsequent notifications of a substantial change or in connection with End of Trial reporting.

The investigator must not make any deviation from or change of the protocol, except which necessary to eliminate an immediate risk to the study subjects, or where the changes only include logistical or administrative aspects of the study (e.g., change of telephone number). Other deviations/changes besides the above-mentioned required agreement with the sponsor and documented approval/favorable opinion regarding the amendment from relevant authorities.

14. Collection, handling, and archiving data

Subjects who participate in the study are coded with a specific study identification number – study ID given by the eCRF. *Certain data cannot be obtained through the quality registries and will be obtained through medical records and entered into the eCRF. Data on women's and their partners' experience of induction will be obtained through self-administered questionnaires. Health economic data such as days in hospital will be collected from SPR and medical records and entered into the eCRF. Interview data will be recorded, transcribed and added to the eCRF. Data in the eCRF will be saved for at least 10 years or as per relevant regulations.*

Source data in the medical records system is stored and archived in accordance with the respective hospital regulations.

14.1. Case Report Form (Forskningspersonsformulär)

An electronical Case Report Form (CRF) is used for data collection. The eCRF is created within the Pregnancy register data-base and stored at least 10 years according to law. The investigator must ensure that data is registered and any corrections in the CRF are made as stated in the study protocol

and in accordance with the instructions. The investigator must ensure that the registered data is correct, complete, and that reporting takes place according to the timelines that have been predefined and agreed. The investigator signs the completed CRF.

If an examination/test is not performed and data does not exist, ND (Not done) or NK (Not known) is marked. If the question is irrelevant NA (Not applicable) is written. Corrections in the eCRF are done by contacting MedScinet striking out the incorrect information, and adding the correct information. The change of data and date for change will be logged in the database.

15. Notification of study completion, reporting, and publication

The Swedish Medical Products Agency shall be informed of the study's completion at latest 90 days after study end, through submission of a "Declaration of End of Trial Notification" form. "Study's completion" in this regard is defined as the last participant answering the three months follow-up by electronic questionnaire.

Within one year after the study is completed, the results regarding the primary outcomes shall be analysed, a clinical study report with individual data shall be prepared, and the study results shall also be reported in the EudraCT database.

If the study is prematurely terminated, the form "Declaration of End of Trial Notification" should only be used if the reason concerns the study's safety. In other cases, it is sufficient that the authorities are informed. If the sponsor terminates an ongoing study, the concerned authorities must be informed as soon as possible, but no later than within 15 days.

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