CLINICAL STUDY PROTOCOL/CLINICAL INVESTIGATION PLAN

OPTION – OutPatienT InductiON

Labour induction in an outpatient setting - a multicenter randomized controlled trial

Study code:	OPTION
EudraCT number:	2020-000233-41
Version number:	3.0
Date:	2020-06-21
Sponsor:	Sahlgrenska University Hospital, Gothenburg, Sweden
Principal Investigator:	Verena Sengpiel

Signature page

Sponsor / 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 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.

Sponsor / Principal Investigator's signature	Date

Printed name

Signature page – template. All signatures provided in Appendix 1.

Responsible Investigator at each site
I have read this protocol and it contains all essential information to conduct this 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 the national and international regulations governing the conduct of this clinical study.

I will submit this protocol and all other important study-related information to the staff members and other involved investigators at this site 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 at this site who work with this study informed and trained.

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

Responsible Investigator's signature	Date

Printed name

Site name

Short summary

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 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.

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.

Method: A national multicentre register-based parallel group randomized controlled trial (R-RCT) performed within 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 have an abdominal palpation and ultrasound scan to exclude malpresentation and oligo- or polyhydramniosis, a cardiotocography (CTG), and a digital cervical exam to establish Bishop score prior to inclusion (as per clinical practice). Randomization will be performed by the attending physician, midwife or study coordinator. Randomization takes place in the hospital after examination of maternal and foetal well-being and screening of inclusion and exclusion criteria (establishment of eligibility). Randomization is not dependent of the method, which is decided upon clinical basis, but only affects outpatient or inpatient care. Blinding is not deemed feasible neither for the patient nor the investigator due to the character of the intervention (inpatient or outpatient care). During statistical analyses allocation will be blinded.

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%.

Aim

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 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.

Background

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.

Objectives
Primary objective
1. To establish if induction in an outpatient setting is as safe for the child (composite outcome for mortality and severe morbidity) as induction in a hospital setting, including low-risk women only.
2. To investigate efficacy of outpatient induction by comparing proportions of women with vaginal delivery in the whole study population as well as in the group of women induced with either balloon or prostaglandin.

Secondary objectives
1. To investigate if other pregnancy and delivery-related outcomes differ between women induced in an outpatient setting versus in a hospital setting including safety, e.g. mother admitted to the intensive care unit, post-partum bleeding >1000 ml, proportion of women delivered vaginally within 24 or 48 hours from start of induction as well as for the children, e.g. the different variables being part of the primary safety composite outcome will be studied individually in form of exploratory analyses.

2. To increase the understanding of women with low-risk induction experiences of induction in an outpatient setting and in a hospital setting by comparison of general self-efficacy (GSE), health-related quality of life (EuroQol-Visual Analogue Scale, EQ-VAS and EQ-5 Dimensions, EQ-5D), pain catastrophizing (Pain Catastrophising Scale, PCS), sense of coherence (SOC), anxiety and depression (Hospital Anxiety Depression Scale, HAD) before randomization as well as 3 months after delivery. Childbirth experiences (Childbirth Experience Scale, CEQ), experiences of the induction, Edinburgh Postnatal Depression Scale (EPDS) and levels of breastfeeding (Breast feeding Efficacy Scale, BSES) will be measured, analysed and compared between groups three months after delivery. In addition, qualitative interviews with 20-25 women will be performed three to six months after delivery.

3. To increase the understanding of partners to women with low-risk induction experiences of induction in an outpatient setting and in a hospital setting by comparison of general self-efficacy (GSE), health-related quality of life (EQ-VAS and EQ-5D), pain catastrophizing (PCS), sense of coherence (SOC), anxiety and depression (HAD) before randomization as well as 3 months after delivery. Childbirth experience (Father for The First-time questionnaire (FTFQ), experiences of the induction and Edinburgh Postnatal Depression Scale (EPDS) will be measured, analysed and compared between groups three months after delivery.
In addition, qualitative interviews with 20-25 partners will be performed three to six months after delivery. In addition, the partners to participating women at Sahlgrenska university hospital will be asked to fill in free-text answers in a qualitative questionnaire three to six months after delivery.

4. To increase the understanding of the healthcare staff's experiences of outpatient versus inpatient induction of low-risk pregnancies by qualitative interviews.

5. To study if induction in an outpatient setting is more cost-effective compared to induction in a hospital setting.

6. To compare future pregnancy outcome in the outpatient and inpatient group.

Study questions in conclusion:

Safety:

- Does outpatient induction differ from inpatient induction in low-risk women with respect to perinatal outcome?
- Does outpatient induction differ from inpatient induction in low-risk women with respect to maternal outcomes?

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?

Risk-benefit and ethical considerations
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 and must give written consent prior to inclusion. 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. We believe that a balanced information can be given in a calm environment. 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.
Participating partners will receive oral and written information in different languages or give their informed consent with the help of a translator prior to inclusion. We believe that a balanced information can be given in a calm environment. 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.

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. In addition to standard care, participating women will be examined with an abdominal ultrasound to identify conditions unsuitable for outpatient induction. Further, women will be asked to contact the hospital immediately if anything starts to feel different. While outpatient induction has not previously been offered in Sweden, it is clinical routine in e.g. the other Nordic countries. 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).

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.

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. 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.

Study design

A national multicentre register-based parallel group randomized controlled trial (R-RCT) 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. 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.

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.

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.

Possible 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

One of the following diagnosis if 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

In- 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

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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)

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<tr><td colspan="2">Based on clinical examination before start of induction including Leopold´s manoeuvres, digital cervical exam, abdominal ultrasound, temperature, blood pressure and CTG scan</td></tr>
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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)

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Small for gestational age (SGA/IUGR/FGA)
Screened for as follows depending on the indication for induction:

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)
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)
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)
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)

exclusion criteria for balloon method
exclusion criteria for prostaglandin method if:

PROM >30 hours
Known colonisation with group B streptococci or previous pregnancy

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	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

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 inclusion criteria and without exclusion criteria, willing to and able to comply with the protocol.

Intervention: Outpatient induction with either balloon catheter or oral prostaglandin.
Women receive either a balloon catheter (Foley catheter, model will be specified, 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 is chosen depending on clinical practice at the study site and follows the guidelines from the Swedish Society of Obstetrics and Gynaecology (SFOG) (33). A CTG will be performed in case of balloon catheter after placement of the catheter. If no immediate adverse events occur within the first 45 min after start of induction, women will be randomized and if allocated to outpatient setting sent home or to a patient hotel. 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.
Women will contact the 24/7 hospital telephone line 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, they will return to the hospital on a booked appointment for further planning of induction according to clinical practice, see below.

Control: Inpatient induction with either balloon catheter or oral prostaglandin.
Women receive either a balloon catheter (Foley catheter, model will be specified, or Cook® Cervical Ripening Balloon) or the first dose of 25 µg misoprostol orally in the hospital (Angusta©). Participating hospitals need to be familiar with the misoprostol preparation used before entering the study, recommended at least one month's clinical experience. The method is chosen depending on clinical practice at the study site. A CTG will be performed in case of balloon catheter after placement of the catheter. If no immediate adverse events occur within the first 45 min after start of induction, women will be randomized and if allocated to inpatient setting depending on the hospital's routine stay at an induction/antenatal care unit or the delivery unit. The balloon will be handled according to the hospital's routine. Oral misoprostol (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 clinical practice, se 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.

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, parent education, and 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. If the woman is eligible and gives her informed written consent, 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. 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 patient will be randomized by a randomization module linked to the SPR.

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. Randomization will be performed by the attending physician, midwife or study coordinator by logging into SPR, see attachment. The attending physician is responsible for the inclusion, information and signing of informed consent, and randomization. Blinding is not deemed feasible; 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.

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)

Treatment
Participating women will be induced as described in the PICO. Possible methods are induction with a balloon catheter or oral misoprostol (Angusta©). Choice of induction method is not specified by the study protocol and will be performed according to clinical routine. 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 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.

Monitoring

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

Outpatient induction: Participating hospitals provide 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

Follow-up in the outpatient group is planned as follows:

1) In case of indication for induction is *not* PROM (a maximum of 2 days spent in the outpatient setting, with clinical control at least every 24 hours):

<table>
<tr><th colspan="2">Day 1 – outpatient</th><th colspan="2">Day 2 – outpatient</th><th>Day 3 – inpatient</th></tr>
<tr><td colspan="2"></td><td colspan="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>Induction continues according clinical routine at the study site.</td></tr>
<tr><td colspan="5">Choice and change of method or decision to stop/pause induction may be made due to clinical routine, the clinician’s judgement, and/or the woman’s preference.
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>Balloon catheter</td><td>Misoprostol:
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.</td><td>Balloon catheter</td><td>Misoprostol:
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.</td><td rowspan="2">Induction continues according clinical routine at the study site.</td></tr>
<tr><td>After balloon application CTG 45 min and observation at the hospital</td><td>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</td><td>After balloon application CTG 45 min and observation at the hospital</td><td>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</td></tr>
<tr><td colspan="4">Oral and written information on when to contact the hospital, booked time for follow-up after a maximum of 24 hours</td><td>Follow-up according to clinical routine</td></tr>
</table>

2) In case of indication for induction is PROM (a maximum of 1 day spend in the outpatient setting):

Day 1 - outpatient	Day 2 - inpatient	Day 3 - inpatient
	Induction continues according to clinical routine at the study site.	Induction continues according to clinical routine at the study site.
Decision to stop/pause induction may be made due to clinical routine, the clinician’s judgement, and/or the woman’s preference. Induction/augmentation of labour with oxytocin infusion may start earliest 4 hours after the last dosage of misoprostol due to the risk of hyperstimulation.		
Misoprostol:		

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.	Induction continues according clinical routine at the study site.	Induction continues according clinical routine at the study site.
First tablet (dose 1) in the hospital, time schedule for the next seven doses (2-8) hour at home		
Oral and written information on when to contact the hospital, booked time for admission to the hospital after a maximum of 24 hours	Follow-up according to clinical routine	

Coding
Participating hospitals will be asked to use the following ICD-10 coding of diagnosis and procedures as follows during the study period:

Z00.6 (Code for study patient). Needs to be registered manually.

All patients randomized to outpatient induction should get the following code at delivery:
Z51.4 Preparatory care for treatment, not elsewhere classified

O61 Failed induction of labour
O61.0 Failed medical induction of labour
O61.1 Failed instrumental induction of labour
O61.8 Other failed induction of labour
O61.9 Failed induction of labour, unspecified

The induction has succeeded if the woman enters active labour, even if no vaginal delivery happens. Hence, O61-codes should only be used if the patient does not enter active labour. In all other cases, codes describing labour dystocia should be used (for example O62.1 secondary labour dystocia). If sequential methods are used, the code used to initiate induction should be used. There should not be two O61-codes.

MAC00 amniotomy (registered manually)
MAC10 cervix dilatation (balloon catheter) is added automatically from the Obstetrix induction template.

All study participants going through induction should have a delivery diagnose code O80-O83.
Sample Size calculation
The study is constructed as a non-inferiority study and hence analysed according to both ITT and Per Protocol of all *randomized* women. Note that randomization is performed late in the induction process and we expect some drop-out between inclusion/consent and randomization, but very a low drop-out rate between randomization and fulfilling the protocol.

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.

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.

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.

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.

3. 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.

4. 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.

Source data and CRF
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 and researchers will only have access to pseudonymized data. Data and the data key will be kept for 20 years to guarantee longtime 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.

Background variables

Background variables will be retrieved by the SPR and eCRF according to the following table.

Variable	Type	Tick box/variable number/ICD code	Data source
Background variables			
Maternal age at time of delivery	Continuous		SPR
Country of birth	Categorical		SPR, SCB Register of Total Population
Professional translator at postpartum visit	Dichotomous (yes, no)		SPR
Occupation	Categorical • work • student • parental leave • seeking work • sick leave • other/unknown		SPR
Self-perceived health before pregnancy	Categorical • very good • good • neither good nor bad • bad • very bad • unknown		SPR
Treatment for being mental unwell	Categorical • yes • no • unknown		SPR
Woman's medical background: Heart disease Psychiatric disease Thrombosis Kidney disease Diabetes mellitus type 1 or 2 Epilepsy Lung disease, asthma Colitis ulcerous, M Crohn Systemic lupus erythematosus Hepatitis Endocrine disease Urinary tract infection Gynaecologic disease Hypertension Other disease	Categorical • yes • no	Tick boxes	SPR
Highest education	Categorical: • shorter than 9 years • at least 9 years primary school • high school 9 to 12 years • university or corresponding • unknown	Tick box	SPR, SCB Education Register
Family income			SCB Income Register
Mode of conception	Dichotomous (spontaneous or ART)	Tick box ICD-10 O26.8A	SPR
BMI at first antenatal visit	Continuous Categorical: • <18.5 (kg/m^2) • 18.5-24.9 (kg/m^2) • 25-29.9 (kg/m^2) • 30-34.9 (kg/m^2) • 35-39.9 (kg/m^2) • ≥ 40 (kg/m^2)	Calculated from height and weight at first antenatal visit	SPR

Cohabitation with partner	Categorical: • yes • no • unknown	Tick box	SPR
Smoking at first antenatal care visit	Categorical: • yes • no • unknown	Tick box	SPR
Self- reported alcohol habits (audit)	Categorical • <7 points • 7-15 points • 16-20 points • >20 points	Tick box	SPR
Length of gestation (weeks and days) at start of induction	Continuous		SPR
PROM	Dichotomous (yes, no)	ICD-10 075.6	SPR
Indication for induction	Categorical (as described above)		eCRF
Reason for not being randomized	Categorical (as described above)		eCRF
Self-estimated time to hospital	Continuous (minutes)		eCRF
Patient hotel	Dichotomous (yes, no)		eCRF

Primary and secondary 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.

Primary outcome 1 is a composite variable for severe child morbidity and mortality including any of the following:			
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

Secondary outcome variables			
The different variables being part of the primary safety composite outcome will even be studied individually in form of exploratory analyses.			
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

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.

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.

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.

3. 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. 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.

5. 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.

Statistics

Populations
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.

1. General Statistical Methodology

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.

2. 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".

3. 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.

4. 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.

6. 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.

7. 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 ≥ 3)
4) depending on indication for induction (PROM versus other than PROM)
5) reported time to hospital < 30 minutes and >= 30 minutes.

8. 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.

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

10. 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).

11. Monitoring
Data safety monitoring board, Monitoring board, and other independent monitoring
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. 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, see attachment.

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.

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 one week for life-threating events and within 15 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.

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. 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.

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.

Clinical relevance, implications

As described above, results from SWEPIS indicating increased perinatal mortality in case of induction at week 42+0 instead of 41+0, have created an immense pressure on Swedish

delivery units to offer induction at week 41+0. We estimate an extra 15.000 inductions/year in Sweden, which cannot just be integrated into the current clinical routine. Several clinics have already decided that outpatient induction is their only option for timely being able to offer general induction at 41+0 weeks. Although outpatient induction is practiced in clinical routine in some of our neighbour countries, scientific evidence regarding the hard and rare outcomes of severe morbidity or death for mother and child is lacking. The NNT by general induction in week 41+0 could be in the same range as the numbers needed to harm by offering outpatient induction. Being able to offer outpatient induction in the context of an RCT as soon as possible is thus asked for by delivery units all around Sweden. Sweden is in the unique position to finally perform an RCT dimensioned for studying the safety of outpatient induction: All clinics face the same challenge right now and randomization and data collection can be achieved without major impact on clinic daily routine thanks to the now well-functioning SPR (R-RCT).

Apart from the possible organizational benefit, several studies have shown that outpatient induction can save a considerable amount of resources for the health care system, resources that could be spend on other more needing health care problems. Based on data from SWEPIS, we know that the average time from admission to delivery was 20.1 hours and from active phase to delivery was 7.13 hours, giving 12.97 hours from admission to active phase of delivery in women induced after week 40+6. Time at the hospital before delivery differed with 6.5 hours between induced women and women with spontaneous onset of labour. For the whole group of low risk inductions, the time from induction start to start of active delivery will probably take even longer when lower gestational ages are included. Outpatient induction may save this time in the hospital. According to SCB there were 114,728 birth in Sweden in 2018. According to the SPR, 19% of all deliveries were induced in 2018. When the majority of pregnancies are induced in week 41+0 instead of 42+0 about 30% of all deliveries will be induced. In our neighbouring countries 42-75% of all inductions are started as outpatient induction. This would mean that about 20.000 inductions/year could be started as outpatient induction in Sweden.

Last but not least, experience from our neighbour countries as well as data from several studies show that women appreciate the choice of where to start the induction. Many women experience outpatient induction as a more “spontaneous” start of delivery, they describe better sleep, nutrition and enjoy the extra time spent in their home and with their family (19, 20).

To summarize, outpatient induction could help winning maternal satisfaction, organizational benefits such as reduced length of stay in hospital, and lower health care costs with the safety of child and mother.

As the study will be run by SNAKS involving most/all of the Swedish delivery units, results are already implemented into clinical routine in case the OPTION trial confirms safety and efficacy of the described outpatient induction protocol. Running a multicentre trial as described will lead to more equal patient care throughout the country. SNAKS itself will develop further by running this trial and facilitate the performance of future trials within the network.

Project organisation
The study is led by an interdisciplinary steering group including:

From Gothenburg:

Verena Sengpiel, MD, Associate Professor, Department of Obstetrics and Gynaecology, Sahlgrenska University Hospital and Sahlgrenska Academy, Gothenburg University
Ylva Carlsson MD, Post Doc, Department of Obstetrics and Gynaecology, Sahlgrenska University Hospital and Sahlgrenska Academy, Gothenburg University
Helen Elden RNM, associate professor, Department of Obstetrics and Gynaecology, Sahlgrenska University Hospital and Institute of Health and caring sciences at Sahlgrenska Academy, Gothenburg University
Ulla-Britt Wennerholm, MD, Associate Professor, Department of Obstetrics and Gynaecology, Sahlgrenska University Hospital and Sahlgrenska Academy, Gothenburg University

From Stockholm:
Helena Kopp Kallner MD, Associate Professor, Department of Obstetrics and Gynaecology Danederyd Hospital
Sophia Brismar Wendel, MD, Post Doc, Department of Clinical Sciences, Karolinska Institutet, Danderyd Hospital
Sofie Graner, MD, Post Doc, Department of Obstetrics and Gynaecology, BB Stockholm
Kristina Gemzell Danielsson, MD, Professor, Department of Women´s and Children´s Health, Karolinska Institutet
Tove Wallström, MD, Post Doc, Department of Obstetrics and Gynaecology, Södersjukhuset

From Falun:
Susanne Hesselman, MD, Post Doc, Department of Obstetrics and Gynaecology, Uppsala University

From Umeå:
Magnus Domellöf, MD, Professor, Dept of Clinical Sciences, Umeå University

Patient representative:
Linda Höglund, Göteborg

Statistician:
Nils-Gunnar Pehrsson, Statistiska Konsultgruppen, Göteborg

Health economist:
Mikael Svensson, HTA-centrum, Göteborg

DSMB:
Lars Ladfors, Senior Consultant and Associate Professor in Obstetrics at Sahlgrenska University Hospital and Chair of DSMB
Göran Wennergren, Professor Emeritus in Paediatrics at Sahlgrenska University Hospital and co-chair
Mia Ahlberg, Head of Midwifery Science and Development at Karolinska University Hospital
Fredrik Granath, Biostatistician, Associate Professor at Karolinska University Hospital,

The study is run as a clinical multicentre study within SNAKS. SNAKS has a vast experience in conducting clinical multicentre studies such as SWEPIS (1), EVA (56), CDC4G (35). VS is vice chairwoman of the SNAKS steering group.

VS, YC, HE, UBW, and SBW are part of the steering groups in several of the SNAKS studies.
VS is member of the steering board for the Swedish Pregnancy Register. YC is a member of the foetal diagnostic register within SPR.
HKK and KGD have vast experience in running pharmaceutical studies.

A study group with representatives from all participant hospitals will be assembled.

Hospitals in other Scandinavian countries might be invited later on when the study is running in Sweden.

Reporting policy and publication
Results will be published in peer-reviewed scientific journals with open access policy. Results will also be presented at national and international scientific meetings. Participating women and partners will be informed about the study results by reporting in mass media. Metanalyses and independent data metanalysis with data from other trials on the topic will be planned in order to gain power for further sub analyses.

Tentative publications

1. The OPTION trial – study protocol on a prospective, randomized, open-label, blinded endpoint (PROBE) trial
2. Safety of outpatient induction – the OPTION trial
3. Outpatient induction with oral misoprostol (Angusta©), a sub-study within the OPTION trial
4. Outpatient induction with a balloon catheter, a sub-study within the OPTION trial
5. Women's experience of outpatient versus inpatient induction of labour respectively, the OPTION trial
6. Health-related quality of life, general self-efficacy, pain catastrophising, anxiety and depression levels, childbirth experiences and breastfeeding in women undergoing outpatient versus inpatient induction of labour respectively, the OPTION trial
7. Health-related quality of life, general self-efficacy, pain catastrophising, anxiety and depression levels, childbirth experiences in partners to women undergoing outpatient versus inpatient induction of labour respectively, the OPTION trial
8. Women's experience of outpatient versus inpatient induction of labour with oral misoprostol respectively, the OPTION trial
9. Women's experience of outpatient versus inpatient induction of labour with a balloon catheter respectively, the OPTION trial
10. Partners' experience of outpatient versus inpatient induction of labour respectively, the OPTION trial
11. Partners' experience of outpatient versus inpatient induction of labour with oral misoprostol respectively, the OPTION trial
12. Partners' experience of outpatient versus inpatient induction of labour with a balloon catheter respectively, the OPTION trial
13. Outpatient induction of labour with oral misoprostol - health cost economics, the OPTION trial

14. Outpatient induction of labour with oral misoprostol - health cost economics, the OPTION
15. Outpatient induction of labour with a balloon catheter - health cost economics, the OPTION
16. Significant factors affecting success of induction of labour at home or in hospital – a secondary analysis of the OPTION trial
17. Subsequent deliveries after outpatient induction, a follow-up of the OPTION trial
18. Subsequent deliveries after outpatient induction with oral misoprostol, a follow-up of the OPTION trial
19. Subsequent deliveries after outpatient induction with a balloon catheter, a follow-up of the OPTION trial
20. Women's and partners' experience of outpatient induction of labour with oral misoprostol (Angusta©), a sub-study within the OPTION trial
21. Women's and partners' experience of outpatient induction with a balloon catheter, a sub-study within the OPTION trial

Metanalyses and independent data metanalysis with data from other trials on the topic will be planned in order to gain power for further sub analyses.

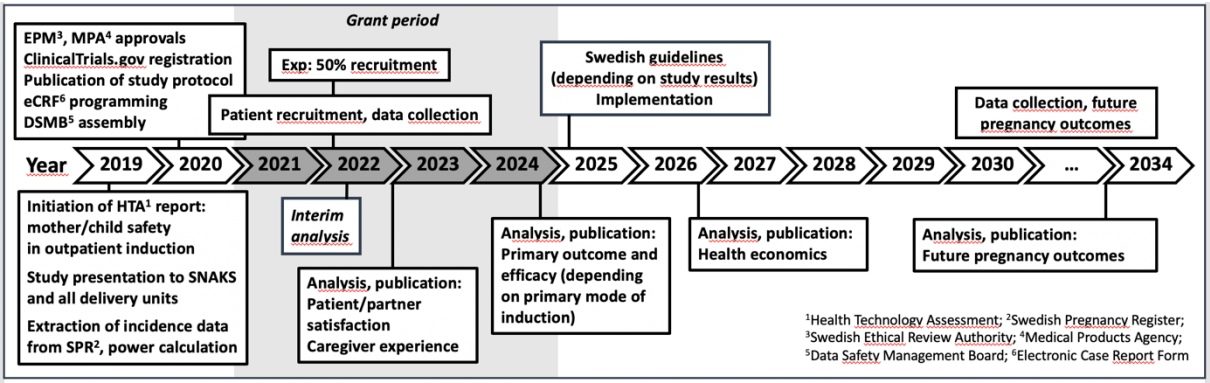
Time schedule

Currently an HTA report is being composed at the HTA centre Gothenburg regarding the question of mother and child safety in outpatient induction to obtain a summary of the available evidence. The conclusion is that evidence regarding safety both for the mother and the child is lacking and that further studies are needed.

Incidence data for the composite outcome have been extracted from the Swedish Pregnancy Register and a power analysis has been run together with Statistiska Konsultbyrån (www.stat-grp.se).

The study has been presented to the SNAKS consortium; a network within the Swedish federation of Obstetrics and Gynaecology supporting national multicentre trials.

Writing study plan and submission to SNAKS, information on the study to all Swedish delivery units
2020 Application for ethical approval. MPA application. Programming of eCRF. Assembly of DSMB. Registration of the Study Protocol at Current Controlled Trials (www.clinicaltrials.gov). Publication of study protocol. Start of recruitment.
2020-2024 Data collection
2021-2023 Analysis and publication of patient and partner satisfaction and healthcare staff experience
2025 Data analysis regarding primary outcome and publication
2030-2034 Data collection and analysis for follow-up on future pregnancy outcomes



Appendix/Attachments
1. Signatures, responsible investigators
2. Study information and consent form
3. Patient information (in Swedish)
4. DSMB charter including SAE report form
5. Questionnaires

Abbreviations

Abbreviation	Explanation
AE	Adverse Event
BS	Bishop Score
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
ICH	International Council for Harmonisation
Induction	Induction of labour
ITT	Intention-to-treat
PP	Per Protocol analysis
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
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

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