Outpatient Balloon vs. Inpatient Gel

oblige

PROTOCOL

Outpatient Balloon vs. Inpatient Gel; a multi-centre randomised controlled trial for induction of labour (New Zealand)

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List of abbreviations

AC = abdominal circumference

AE = adverse event

ARM = artificial rupture of membranes

CF = consent form

CRF = clinical report form

CTG = cardiotocography

DSMC = Data and Safety Monitoring Committee

EFW = estimated fetal weight

FGR = fetal growth restriction

HC = head circumference

IOL = induction of labour

IV = intravenous

LMC = Lead Maternity Carer

NICU/SCBU = Neonatal Intensive Care Unit/Special Care Baby Unit

NPRS = numeric pain rating scale

NZ = New Zealand

PG = prostaglandin

PI = primary investigator

SAE = serious adverse event

SRM = spontaneous rupture of membranes

1. Summary

Induction of labour (IOL) is a common intervention in childbirth. Initiating IOL with vaginal prostaglandin hormone is the preferred method [1] and is current standard of care in New Zealand (NZ). Due to its potential clinical risks, it requires ongoing assessment in hospital. Many trials show that initiating IOL with a mechanical method, such as a balloon, has fewer associated risks than prostaglandins, and is as effective at achieving a vaginal birth. Small trials show that initiating IOL out of hospital is feasible and acceptable, and women are satisfied with this method. Outpatient care may also be of benefit to a busy women's health service in terms of staff, beds, and overall costs. However, low-risk women are not yet offered the option of having a balloon and spending the first part of their induction out of hospital. Outpatient IOL with balloon compared to standard care has not yet been adequately studied for effectiveness and safety. However, in one small trial, women who initiated their labour with outpatient balloon did have a lower caesarean rate compared to inpatient balloon. We hypothesise that women initiating their IOL at home with a balloon compared to prostaglandins in hospital will have a lower risk of emergency Caesarean due to fewer complications, due to women feeling more rested and calm at the start of their labour, and due to clinicians feeling less pressured to intervene earlier ("out of sight, out of mind"). We further hypothesise that women will be more satisfied with this method, that it will be acceptable to both women and staff, and that it will be as safe as standard care.

2. Background

Introduction: In NZ, IOL is a very common intervention in childbirth. IOL is defined as the artificial initiation of labour;[1] the alternative is expectant management of the pregnancy where spontaneous labour is awaited. Induced labour has an impact on the birth experience of the woman. It may be perceived as more painful, and more women will get an epidural. It may be less efficient, and more women will have an instrumental vaginal birth or an emergency caesarean delivery. Other common complications associated with IOL for the mother include uterine hyperstimulation and post-partum haemorrhage.

IOL is offered when evidence shows that benefit to mother and/or baby outweighs the risk. The target population is pregnant women who develop a maternal, fetal or obstetrical risk or

complication where expedited delivery would be considered. A common example would be a woman whose pregnancy has gone one week past the due date. The outcome usually measured in studies evaluating IOL is vaginal birth achieved within 24 hours.

In NZ in 2015, 24% of pregnant women had an IOL.[2] At Auckland Hospital, the largest maternity hospital in NZ, one in three women who gave birth in 2016 had an IOL,[3] equating to six women per day for all 365 days of the year. Half of the beds on the acute women's assessment unit can be taken up by women undergoing IOL, as each IOL takes 12-72 hours. Acute assessments of patients who are unwell may be delayed due to lack of beds in the unit. The significant physical and human resource dedicated to women having IOL therefore has the potential to impact on the provision of safe and efficient care to all women accessing maternity services. Bed block in acute women's assessment unit also carries with it the risk of breaching the Emergency Department 'six-hour rule,' one of the Ministry of Health's key health targets and an important indicator of the health system's performance.[4] At the patient level, there are regular complaints about their IOL experience.

Our research partnership decided to approach this problem creatively by considering whether it would be effective and safe to allow women to be managed out of hospital during the initial part of IOL using the more novel option of balloon induction, instead of current practice using traditional pharmacological methods and remaining in hospital throughout. We will present the evidence that the outpatient approach is acceptable to women and that using a balloon reduces clinical complications. We will then make the case that the alternative approach of combining both outpatient care and balloon method of IOL would be of significant benefit to pregnant women, whilst also reducing hospital costs, and is the way forward.

Prostaglandin method of induction of labour: This method begins with one or more doses of prostaglandin E2 placed into the vagina, in order to make the cervix soft, thin and open, i.e. ready for induction. This is followed by artificial rupture of membranes (breaking the waters) and an intravenous (IV) oxytocin infusion. Vaginal prostaglandins (PGs) as an induction method are more effective than placebo at achieving vaginal birth within 24 hours.[5] However, vaginal PGs are associated with the complication of uterine hyperstimulation.[5]

Mechanical methods of induction of labour: There is high quality evidence from randomized trials that mechanical methods (such as a balloon catheter) are a safe and effective alternative to pharmacological methods to initiate the IOL process. Mechanical methods work by provoking the release of a woman's naturally occurring PG hormones. The Cochrane review on mechanical methods included 17 trials (1,894 women) comparing induction with mechanical method, such as balloon catheter, to vaginal PGs.[6] Women having IOL with balloon had less uterine hyperstimulation with fetal distress (0% vs 5%, risk ratio 0.16 (0.06-0.39)), and less instrumental vaginal births (21% vs 27%, risk ratio 0.79 (0.64-0.98)). Balloon inductions were associated with more oxytocin usage (75% vs. 50%). Both methods had comparable rates of vaginal birth within 24 hours, and of caesarean delivery.

Outpatient induction of labour: There are potential benefits to managing IOL as an outpatient. Women may prefer spending more time in the privacy and comfort of their own home, eating, drinking, and sleeping normally. Three trials show women's preference for, and satisfaction with, outpatient management.[7,8,9]

There is some evidence from randomised trials that initiating IOL out-of-hospital is a safe and effective alternative to in-hospital IOL. The Cochrane review included four trials comparing outpatient to inpatient labour induction, but results were not pooled in a meta-analysis in view of the fact that each study used a different method to induce labour.[10] Three used PGs;[7,11,12] one used a balloon catheter.[13]

Sciscione et al. randomised 111 women in two American tertiary referral hospitals to outpatient vs inpatient balloon and found no differences between the groups in their primary outcome (change in Bishop score) or secondary outcomes.[13] There were no adverse events or maternal morbidity. As expected, women in the outpatient group spent 10 fewer hours in hospital. A surprise finding was that fewer women in the outpatient group had a caesarean delivery [29% vs. 43%, RR 0.67 (95% CI 0.41-1.10)]. The authors suggested this may be attributed to clinician and patient perception of a longer IOL process in the inpatient group which might have led to making a diagnosis of "failed induction" earlier in the inpatient group.

The authors of the Cochrane review called for more trials examining IOL in outpatient settings to assess its safety and effectiveness.[10]

Only one small trial has been published to date on our specific research question. Henry et al. randomised 101 women in an Australian tertiary hospital to outpatient balloon versus inpatient vaginal prostaglandins to assess feasibility, clinical effectiveness and acceptability.[9] Women randomised to outpatient balloon were less likely to achieve vaginal birth within 12 hours of admission (28% vs. 53%, p=0.01); however, they had comparable rates of caesarean (34% vs. 29%, p=0.6). They spent 11 fewer hours in hospital before the birth, had less discomfort (26% reported feeling a lot of discomfort vs. 58%, p=0.03) and more hours of sleep (5.8 vs. 3.4, p<0.01), felt more able to relax (p=0.01) and to rest (p=0.01), and were more likely to choose this method again (65% vs 42%, p=0.03).

Explanation for choice of comparators: In NZ, most women start their IOL with vaginal PGs and remain in hospital throughout. Given the potential risk to the fetus of uterine hyperstimulation with abnormal fetal heart rate changes (5%) requiring repeated maternal and fetal assessment, we did not want to offer women outpatient IOL with vaginal PGs. Balloon IOL, on the other hand, appears safe and effective, is not associated with hyperstimulation (0%), and does not require regular assessment. Outpatient IOL is associated with higher patient satisfaction. Thus we decided to offer outpatient balloon induction as the alternative to standard care.

Objective: To demonstrate clinical effectiveness, safety and cost effectiveness for mothers and babies who are allowed to go home after commencing balloon IOL, versus remaining in hospital after commencing vaginal prostaglandin IOL.

3. Hypothesis and aims

Primary hypothesis: Women having outpatient IOL with balloon will have a lower caesarean section rate compared to women having inpatient IOL with vaginal PG.

Secondary hypotheses: Compared to inpatient IOL with vaginal PG, outpatient balloon IOL will not result in increased adverse events for mother or baby; that women having outpatient balloon IOL

will be more satisfied; that staff looking after women having outpatient balloon IOL will be more satisfied; and that outpatient balloon IOL will be more cost effective.

Primary Aim: To assess the effect of outpatient balloon compared to inpatient vaginal PG as initial management of IOL on the caesarean rate in low risk women having IOL at term.

Secondary Aims: To assess other outcomes in women having initial management of IOL with outpatient balloon compared to inpatient vaginal PG:

- Vaginal birth within 24 hours
- Maternal adverse and serious adverse events
- Fetal/neonatal adverse and serious adverse events
- Maternal post-partum satisfaction with IOL process
- Staff satisfaction with caring for women having IOL
- Cost effectiveness

4. Safety

4.1 Potential risks of IOL (for definitions, go to Section 14.2)

Cord prolapse – This is an uncommon occurrence in labour and is more likely to occur after artificial than spontaneous rupture of membranes if the baby's head is not fully engaged.

Uterine rupture – This is a rare occurrence in labour in the absence of previous caesarean, but is reported to occur more often in IOL compared to spontaneous labour.

Post-partum haemorrhage – This is reported to occur in about 6% of women having initial management of IOL with vaginal PG gel, compared to 4% in women having balloon.[6]

Uterine hyperstimulation – This is reported to occur in about 5% in women having initial management of IOL with vaginal PG gel, compared to 0% in women having balloon.[6] This can also occur during oxytocin infusion.

4.2 Potential risks of outpatient management

Participants out of hospital could spontaneously establish in labour or have their membranes rupture, and will not have immediate recourse for fetal assessment as they would if in hospital. We will be providing women with a written pamphlet on what to expect at home, and to return if these occur (See Appendix 2). In one outpatient trial, one woman out of 101 was erroneously told to remain at home when she developed regular contractions, and fetal monitoring was abnormal when she finally presented back to hospital.[9] The baby was delivered by emergency caesarean in good condition. This underscores the importance of the hospital clinicians checking to see if a woman phoning the hospital for advice is in the study and providing appropriate advice.

4.3 Potential risks of balloon catheter

A recent systematic review was performed of 26 studies (21 of which were RCTs) of balloon IOL to assess the complication rate during cervical ripening.[21] Events included: pain/discomfort (0.26%), unintended amniotomy (0.04%), vaginal bleeding (0.07%), balloon displacement (0.07%), and non-reassuring fetal heart rate (0.01%). Other rare events that occurred to only one to three women out of 8,292 included: allergic reaction, balloon rupture, reduced fetal movements, voiding problems, uterine hyperstimulation, and non-cephalic presentation at the time the balloon was removed. There were no events of intrapartum infection, cord prolapse, abruption, uterine rupture, fetal death or maternal death. Some adverse events resulted in a caesarean, but mostly the IOL was continued without any concerns. The authors concluded that the risk of adverse events during the period between insertion and expulsion of a balloon catheter in cervical ripening was low, and that the data facilitate further evaluation and implementation of this procedure in an outpatient setting for low-risk pregnancies.

5. Study design

OBLIGE is a multi-centre randomized controlled trial with intention-to-treat analysis. Participants will be recruited from maternity hospitals across NZ. Each hospital will nominate local investigator teams of obstetricians, midwives and neonatologists to oversee local recruitment. The OBLIGE trial

will be coordinated by the Principal Investigator (PI), the OBLIGE Trial Steering Committee, the Data and Safety Monitoring Committee (DSMC), the Local Lead Investigators, and the OBLIGE Research Midwife.

Participating centre and contract site number	**Local Lead Investigator**	**Contact details**
Auckland 9180	Dr Jenny McDougall	JennyMcD@adhb.govt.nz
Tauranga 9320	Dr Chris Thurnell	Chris.Thurnell@bopdhb.govt.nz
Waikato 9382	Dr Joy Marriott	Joy.Marriott@waikatodhb.health.nz
Wellington 9687	Dr Rose Elder	Rose.Elder@ccdhb.org.nz
Hawkes Bay 9510	Dr Kirsten Gaerty	Kirsten.Gaerty@hawkesbaydhb.govt.nz
Whakatane 9675	Dr Thabani Sibanda	Thabani.sibanda@bopdhb.govt.nz
Nelson 9220	Dr Alice Pan	Alice.pan@nmhs.govt.nz
Taranaki 9520	Dr Valentina Shaw	Valentina.Shaw@tdhb.org.nz
Hutt Valley 9610	Dr Meera Sood	Meera.sood@huttvalleydhb.org.nz
Waitemata 9820	Dr Premjit Gill	premjit.gill@waitematadhb.govt.nz
Potential future sites		
Dunedin 9485	Dr Michael Stitely	michael.stitely@otago.ac.nz

6. Study population

6.1 Inclusion criteria:

- Pregnant women with live singleton cephalic presentation;
- Planning IOL at ≥ 37 weeks gestation;
- On admission for IOL:
    - Intact membranes
    - Bishop score < 7
    - Cardiotocography (CTG) normal
- Willing to remain within 1 hour of hospital, if allocated outpatient balloon;
- Speaks enough English to communicate with hospital midwife by phone, or has someone with her who does, if allocated outpatient balloon.

Essentially, any pregnant woman who has been managed as an outpatient until the point of IOL would be considered eligible for this study. Indications include: post-dates, slowing of growth, diabetes in pregnancy, hypertension in pregnancy, large for gestational age, antepartum haemorrhage, reduced fetal movements, oligohydramnios, late maternal age, obesity, in vitro fertilisation pregnancy, obstetric cholestasis, maternal request.

6.2 Exclusion criteria:

- Previous caesarean, as PGs would be contraindicated;
- Major fetal congenital anomaly;
- Severe fetal growth restriction (FGR)*, as PGs would be contraindicated;
- Maternal condition (such as preeclampsia), or fetal condition, where the clinician feels outpatient care would be contraindicated.

* Severe FGR defined for the purpose of this study as: customised EFW < 3%; FGR and oligohydramnios; or FGR and abnormal Doppler indices (umbilical artery, uterine artery, middle cerebral artery, or cerebro-placental ratio).
* FGR defined as: AC ≤ 5%; discrepancy between HC and AC; customized EFW < 10%; or AC or customized EFW crossing centiles.[14]

6.3 Participant withdrawal from study after randomisation

Participants can choose to withdraw from the study at any time. Data collected up to that point will be retained and used as part of the intent to treat analysis.

At the time of withdrawal, the local investigator is encouraged to ask the participant if they would be willing to continue participating in a more limited way. For example, they may no longer wish to continue with their allocated method of IOL, but they may be willing to have their data collected until they and their baby are discharged home from hospital after the birth. This limited level of participation must be recorded in REDCap in the Study Management Form. In addition, it would be helpful to record the reason for withdrawal from the study.

7. Study numbers and Sample size calculation

7.1 Sample size calculation

At Auckland Hospital in 2015, the caesarean section rate in women who had IOL (excluding women with previous caesarean) was 24.8%, almost all of whom had vaginal PG gel.[3] In the small published trial of outpatient vs inpatient balloon IOL, the caesarean rate decreased from 43% to 29% (a relative risk reduction of 32%).[13] Based on consultation with local and Australian obstetricians and researchers, we felt that a 6% absolute decrease in caesarean rate would be a clinically meaningful difference. In order to detect a decrease in caesarean rate from 24.8% to 18.8% (a relative risk reduction of 24%), with 80% power and a two-sided type 1 error of 0.05, the sample size required would be 743 women for each study group. Adding a continuity correction, the **total sample size required is 1,552 women.**

7.2 Feasibility

There are currently 11 hospitals collaborating in this trial. Based on the Auckland Hospital 2015 Annual Clinical Report,[3] we estimate about 40% would be eligible for this trial. Based on previous trials, we estimate 60% of eligible women would consent to participate. We additionally account for 5% drop out between randomisation and collection of primary outcome data. This would result in

1,284 participants per year. Recruitment would therefore be expected to take about 16 months. Two more hospitals are considering joining the trial, which would shorten recruitment time.

Site	**Month of 1st recruited participant**	**Total number participants (to 30 September)**	**Monthly target**
Auckland	Oct 2017	103	36
Tauranga	Dec 2017	36	11
Wellington	March 2018	25	16
Waikato	April 2018	21	8
Hawkes Bay	May 2018	12	6
Whakatane	May 2018	1	4
Taranaki	July 2018	2	8
Hutt Valley	September 2018	2	6
Nelson	Just started recruiting		6
Waitemata	Not yet recruiting		9
Total		**202**	**110**

8. Participant selection and Recruitment:

At the point an IOL is recommended, the clinician will identify if the woman is eligible for the study, and if so, will discuss the OBLIGE Study with the woman and provide her with the Patient Information Sheet and Consent Form (CF). She will be given time to consider and discuss with her midwife, family and whanau as needed. Contact information for the local investigators will also be provided. Local lead investigators will follow up with the woman and if she does wish to participate in the study, then the CF will be signed.

In addition, the local research team can regularly screen all induction bookings for eligibility, and identify potentially eligible women to the consulting obstetrician or lead maternity carer (LMC).

On the day of IOL, women will present to hospital and the clinician will confirm the woman meets the inclusion and exclusion criteria and still wishes to participate in the study. CF will be signed if it hasn't already. The signed consent form will be kept with the other data collections forms (to be scanned and uploaded to REDCap), a copy put into the woman's notes, and another copy to her.

The woman will have an admission history, exam, and CTG by the clinician, as per usual hospital practice. History includes estimated date of delivery and parity. Exam includes a sterile digital vaginal cervical assessment to determine the modified Bishop score.

Confirmation of eligibility: If Bishop score is 7 or greater, she does not need balloon or PG, and will not be eligible for the study. If the CTG is abnormal, she will not be eligible for the study. If membranes have ruptured, she will not be eligible for the study.

SCREENING LOG: Local research teams are asked to keep track of all women who have IoL and determine if they were eligible for OBLIGE, if they were approached to participate, if they accepted or declined to participate, and if they got randomised to OBLIGE or were missed – these data will contribute to the CONSORT diagram (Figure 1). If women decline, please enquire the reasons so we can optimise recruitment strategies.

9. Randomisation

If woman meets all inclusion and exclusion criteria, and CF has been signed, then the clinician or local investigators will perform the web-based randomisation. Centralised online randomisation will occur at www.ligginstrials.org/oblige/.[15]

Randomisation training Site

https://www.ligginstrials.org

Site access: 991000tst

Summary View (Admin): tst000199

The randomisation schedule was prepared by the OBLIGE Trial Steering Committee. Randomisation is stratified for:

- Participating centre, and
- Parity (nulliparity or multiparity) (if unknown by DHB, then default 50/50)

Randomisation has no restrictions. Allocation is on a 1:1 ratio to outpatient balloon:inpatient PG. The randomisation process will assign each participant with a unique Study ID Number. If a woman is found not to be eligible for the study when her details are entered into the randomisation program, the program will return a screen failure notification.

If randomisation online site is down, contact Michelle Wise, Paula Harre or Mariska Oakes-Ter Bals for offline randomisation instructions.

10. Treatment groups

Women will be randomised to one of two groups:

1. Outpatient balloon x 18-24 hours
2. Inpatient vaginal PG

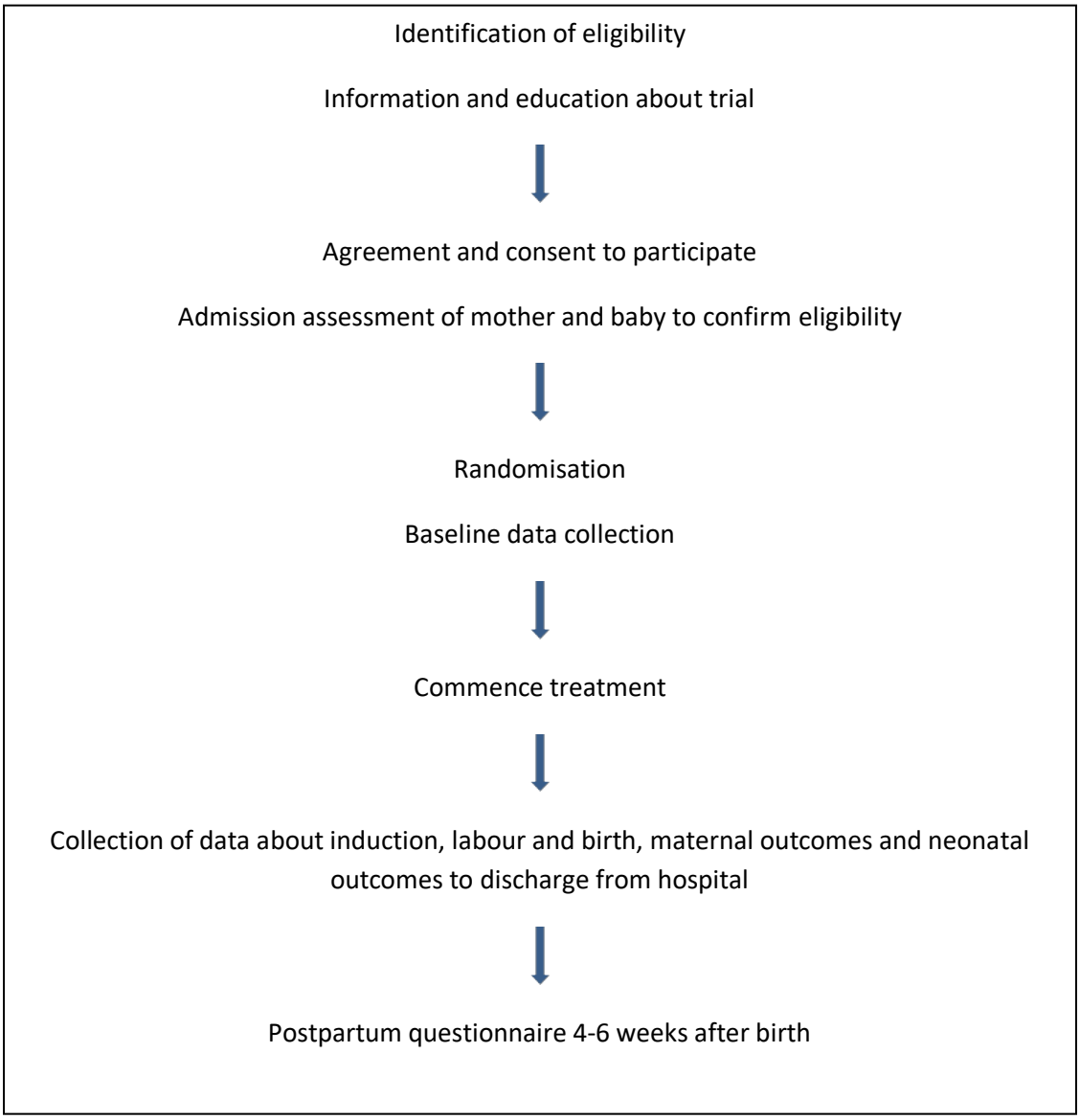
Treatment will commence as soon as possible following randomisation. However, if the woman, her LMC or the hospital maternity service prefers a delay to starting treatment, this is reasonable as long as treatment starts on the same day as randomisation.

Participants and clinicians are not blinded to treatment allocation; however, the outcomes are objective, and most data are routinely collected for clinical care.

Concomitant procedures during IOL such as membrane sweeping, and milk expressing, can go ahead if this is part of the usual care of the woman.

11. Study procedures and participant flow chart

Individual participant study flow chart



11.1 Baseline data collection

The clinician informs the woman of her study group, and asks her to complete the Maternal Enrolment Survey, which includes questions on ethnicity and type of LMC. The clinician collects baseline data including: height and weight, primary reason for IOL, and initial Bishop score.

11.2 Outpatient balloon group

The clinician will perform a sterile speculum exam (may be facilitated with woman in lithotomy) and cleanse the cervix. Alternatively, bimanual exam can be performed. Place the Foley single balloon catheter through the cervix to above the internal cervical os. The balloon will be inflated with 50mL sterile water. The study balloon is: HAEMATURIA 2 WAY FOLEY CATHETER 20F 2550H20CE 30/50mLs. The alternative balloon is: FOLEY CATHETER 16F 166816CE 30mLs, which is silicone (latex free), and can be inflated to 50mL (though off-label). The balloons can be ordered from Bard. Contact Health Alliance to order at study price.

The catheter will be secured to the medial thigh on slight tension. The woman does not need a routine CTG after placement, unless there is clinical concern, or in order to comply with local hospital protocol. Clinician to show the woman the pain scale and ask her to rate her discomfort with placing the balloon using the following statement, and document the response.

Please rate your discomfort, from 0 which is "no pain" to 10 which is "worst possible pain"

NOTE: If clinical concern arises, such as vaginal bleeding during balloon insertion, clinicians can choose to keep the participant in hospital for observation (for a few hours, or for the full 18-24 hours). These participants are still in the trial, should continue to follow study protocol, and should still have all their data collected and documented. This is not an allocation error.

If unable to insert the balloon, or it falls out within a few minutes, clinician can choose whether to change to 2nd method (PG) or progress to ARM or oxytocin. Balloon is still reported as 1st method.

The woman will receive detailed verbal information about what to expect, to return to the hospital at any time if she has spontaneous rupture of membranes (SRM), contractions, vaginal bleeding or decreased fetal movements, and to contact the hospital midwives if concern. The woman will also

receive the OBLIGE written pamphlet on outpatient balloon (Appendix 2) and then be discharged from the hospital with instructions to return at a specified time, around 18-24 hours after balloon placement. The woman does not have to go 'home' per se, rather she is welcome to stay nearby the hospital in a motel-like setting or with friends/family (though not funded by OBLIGE Trial).

If participant returns to hospital earlier than planned due to SRM, then balloon should be removed. If participant returns for any reason, she and the baby should be assessed, and the clinicians can decide if she can go back home and return at the original pre-specified time, or remain an inpatient. The balloon should not remain in situ longer than 24 hours.

Midwife can routinely ring the woman in the evening to see how she is getting on and if there are any questions or concerns, and confirm time to return to hospital.

From the time of return to hospital, the woman will remain an inpatient. The midwife will remove the balloon (50mL), and perform a CTG and an artificial rupture of membranes (ARM) if appropriate. If this is not possible, then the duty medical officer will attempt to do so. The time and date of balloon insertion and removal will be documented.

Clinician to show the woman the pain scale and ask her to rate her discomfort with ARM using the following statement, and document the response.

Please rate your discomfort, from 0 which is "no pain" to 10 which is "worst possible pain"

If ARM is still not possible or appropriate, then the woman will receive PG (2nd method of cervical ripening) and remain an inpatient. Follow study protocol.

The participating centres have all agreed that LMCs <u>may</u> provide but will not be expected to provide clinical care to participants during the initial part of their IoL, even while outpatient.

The participating centres have all agreed that outpatient IoL with a balloon will not be offered to women eligible for the study outside the study for the duration of the study.

11.3 Inpatient PG group

The clinician will place a Prostin PG gel or Cervidil PG sustained-release insert in the vagina during a vaginal cervical assessment. Either type of vaginal PG is appropriate. The woman does not need a routine CTG after placement, unless there is clinical concern, or to comply with local hospital protocol. Clinician to show the woman the pain scale and ask her to rate her discomfort with placing the first vaginal PG using the following statement, and document the response.

Please rate your discomfort, from 0 which is "no pain" to 10 which is "worst possible pain"

The timing and dose of each PG gel/insert can be at the discretion of the clinical team, taking into account parity and Bishop score. Each PG gel/insert should be prescribed on the National Medication Chart. CTG monitoring will be as per hospital protocol.

The assessment and administration of PG gel/insert will be repeated regularly (not < 6 hours apart for gel; not < 12 hours apart for insert) until ARM is possible and appropriate, or if labour establishes spontaneously, or SRM, or if patient/clinician prefer to switch to balloon, or to a maximum of 6 doses for gel; maximum of 2 doses for insert. The date and time of the first and last PG gel/insert will be documented. If unable to do ARM, and unable to insert balloon, then for clinician to decide how to proceed.

At time of ARM, clinician to show the woman the pain scale and ask her to rate her discomfort with ARM using the following statement, and document the response.

Please rate your discomfort, from 0 which is "no pain" to 10 which is "worst possible pain"

At any point that the woman starts to feel regular painful contractions, the midwife will perform a CTG. If ARM is still not possible or appropriate, then she will receive a balloon (2nd method of cervical ripening) and remain an inpatient. Do not switch to different type of PG. Follow study protocol.

The participating hospitals have all agreed that the vaginal PG administration will be managed as per study protocol even if it differs from their "usual care."

11.4 Common protocol to both study groups

If after both methods (balloon and PG), still unable to do ARM, then for clinician to decide how to proceed.

Following ARM or SRM, in the absence of spontaneous onset of strong, regular, painful contractions within 1-2 hours, intravenous oxytocin infusion will be started and titrated to contractions, according to local hospital protocol. It should not be started < 6 hours from last PG gel; <12 hours from placement of last PG insert. Date and time of starting oxytocin will be documented. Analgesia will be administered at maternal request as per local practice. Continuous electronic fetal monitoring is recommended whilst on oxytocin infusion.[16] Labour will be managed by the hospital clinician or participant's LMC, as per local practice.

Recommendations from the research steering group about management of labour:

1. Study definition of established/active labour = regular, strong, painful contractions and cervix dilated 4 cm or more
2. Routine intrapartum care as follows:
    a. 1st stage established/active labour - cervix exams for progress every 2-4 hours and "slow progress" warrants medical reassessment, defined as < 0.9cm/hour in a primip and < 1.2cm/hour in a multip.
    b. 2nd stage - cervix exam for descent every hour and "prolonged second stage" warrants medical reassessment, defined as > 2 hours in a primip (3 with epidural) and > 1 hour in a multip (2 with epidural).[17]
3. Oxytocin – there are low-dose and high-dose protocols. Low-dose begins with 1-2 mU/min increased incrementally by 1-2 mU/min at 30-minute intervals; high dose begins with 4-6 mU/min increased incrementally by 4-6 mU/min at 15-30 minute intervals. Benefits of low-dose include less risk of uterine hyperstimulation and use of smaller overall dose, with no difference in vaginal birth within 24 hours, caesarean delivery, induction to delivery interval, or serious maternal or neonatal morbidity.[18] Choice of protocol is at the discretion of the clinical site.
4. If Occiput Posterior diagnosed in 2nd stage, consider attempting manual rotation

5. Intrapartum Fetal Surveillance Clinical Guideline should be followed for management of fetal heart rate abnormalities (Recommendations 8 and 11-13).[16]
6. **Cord lactate and/or gases will be taken routinely on all OBLIGE Study babies.**

11.5 Concomitant clinical management and co-intervention

Clinical care to participants will be provided by multiple clinicians throughout their induction, labour, birth and post-partum. It is up to the discretion of the clinician if, for example, during a cervix assessment, they wish to additionally perform membrane sweeping.

11.6 Outcome data collection

Local investigators or hospital clinician will collect data on participants at three time points. The first is at time of IOL; the second is at time of birth; the third is post-partum/discharge from hospital. Data will also be collected on the neonate at two time points; at time of birth, and at discharge from hospital.

Some questions will be asked directly to women. Most data will be collected contemporaneously by the clinicians looking after the woman; most of these data are collected already for usual clinical care. Some data may need to be collected retrospectively from the medical records if forms are incomplete. Pain scores should not be asked in retrospect, it is preferable for the data to be missing than to ask women to remember their pain score well after the fact.

In addition, for the outcome of uterine hyperstimulation, the local investigators will retrospectively review the CTGs of every participant to standardise this important outcome.

A maternal post-partum questionnaire will be carried out at 4 weeks after the birth. If the woman has agreed to this at time of enrolment, it will be done by email direct to women through REDCap, followed by two automatic email reminders at 5 and at 6 weeks if needed. Research team can also ring or text participants as a reminder and to ensure email address is correct. If the participant has indicated a different preference for receiving the post-partum questionnaire, then it is the responsibility of the local investigators to arrange telephone questionnaire, or print and post with stamped return envelope.

A staff satisfaction questionnaire will be carried out at 6-monthly intervals during the study at participating centres. This will also be done by email direct to staff from the Auckland research team, as long as the local investigator provides staff emails. If not, then it will be up to the local investigators to take responsibility for completion of the staff questionnaires and data entry.

12. Safety assessment and monitoring (for definitions, go to Section 14.2)

12.1 Assessment of adverse events (AEs)

Information will be collected regarding all AEs that occur from the time of randomisation until maternal hospital discharge after the birth, and until neonatal hospital discharge. AEs will be compiled by the trial statistician and the OBLIGE Project Manager into a written report on a six-monthly basis, and provided to the Chair of the DSMC.

In all women undergoing IOL, some complications are anticipated outside of trial participation. Investigators should take this into account when assessing potential AEs. The following events do not need to be reported, unless the investigator considers it to be possibly, probably, or definitely related to participating in this trial:

- Chorioamnionitis in labour
- Antepartum haemorrhage
- Post-partum haemorrhage
- Post-partum endometritis
- Neonatal birth injury
- Neonatal admission to NICU/SCBU
- Neonatal infection

12.2 Assessment of serious adverse events (SAEs)

The following events are considered SAEs and need to be reported (See 12.4):

- Cord prolapse
- Maternal admission to intensive care unit or equivalent
- Maternal death

- Fetal death/stillbirth
- Neonatal encephalopathy, moderate-severe
- Neonatal death, early

12.3 Investigator review of AEs/SAEs

The following are the minimum parameters to be collected for each event:

- Duration: when the event started and ended (date/time)
- Action taken: did the event cause the study intervention to be discontinued?
- Relationship to study intervention: the investigator will determine if the intervention contributed to the AE/SAE
- Treatment given: provide as many details as applicable

12.4 Procedure for AE and SAE reporting

The Local Lead Investigator, within 48 hours of becoming aware of an SAE, must notify the PI by phone and/or email and complete the SAE report in REDCap. Alternatively, the SAE report can be completed in hard copy, scanned and emailed to **oblige.study@auckland.ac.nz.** The PI will review the SAE and report it to the Chair of the DSMC by email within 48 hours of becoming aware of the event. All events must also be documented in the participant's notes.

PI Contact Details: Dr Michelle Wise 021-302-978 **m.wise@auckland.ac.nz**

12.5 Data Safety and Monitoring Committee (DSMC)

The DSMC for the OBLIGE Trial is chaired by Professor Lesley McCowan, Department of Obstetrics and Gynaecology, Faculty of Medical and Health Sciences, University of Auckland, and includes Dr Chris McKinlay (Neonatologist) and Dr Ngaire Anderson (Obstetrician). The DSMC reports to the PI. Terms of Reference for the DSMC were confirmed on 24/10/2017.

13. Confidentiality and Data Collection

Data will be collected on clinical reporting forms (CRFs) using the participant's Study ID Number to ensure confidentiality for each woman and her baby. Data will be entered onto hard copy CRFs by clinicians, and into the electronic REDCap Database developed for the OBLIGE Study by the local research team.[19]

REDCap Access
Quick link: https://redcap.fmhs.auckland.ac.nz/

Generic accounts - reduced access level.

Data entry
Basic user instructions on Hub Wiki:
https://wiki.auckland.ac.nz/display/ontrack/Creating+Records+and+Entering+Data

Once the data entry into REDCap is complete (labour and birth, and maternal and neonatal complications), **the local team will scan and email the data collection forms to the OBLIGE research team (oblige.study@auckland.ac.nz)**.

The OBLIGE research team will check the entered data using the scanned data collection forms, and if any incomplete data or queries, they will communicate with the local team through REDCap. Once data entry is complete, the OBLIGE research team will lock the forms.

Eight weeks after the date of delivery, even if post-natal survey is incomplete, then the post-natal survey form will be locked by the OBLIGE research team. At that point, the case is considered complete. The local team should invoice the Auckland DHB Research Office for the payment-per-recruit (as per Clinical Research Trial Agreement) on a quarterly basis.

Signed consent forms and hard copy maternal enrolment surveys will also need to be submitted to the Auckland research team, as these contain personal identifying data on participants. These can be sent by post on a quarterly basis. This information will be stored in the Department of Obstetrics and Gynaecology for 10 years, under the responsibility of the PI.

14. Outcome measures

14.1 Primary outcome: Caesarean section

The proportion of participants who give birth by Caesarean will be compared between the two study groups.

14.2 Secondary outcomes:

Maternal:

1. discomfort during placement of balloon/1st PG;
    a. NPRS, from 0 (no pain) to 10 (worst possible pain)
2. for balloon: duration in situ, removed or fell out, early unplanned return to hospital and reason;
    a. reasons include: spontaneous contractions, SRM, decreased fetal movement, vaginal bleeding, any concern, convenience, balloon fell out, advised by clinician, other
3. total number of PG gels given;
4. need for second method of cervix ripening, reason;
    a. reasons include: unable to do ARM, unable to place balloon successfully, clinician or participant preference, other
5. need for ARM, discomfort during ARM;
    a. NPRS, from 0 (no pain) to 10 (worst possible pain)
6. uterine hyperstimulation, if treatment was required;
    a. hyperstimulation is defined as tachysystole (> 5 contractions in 10 minutes) or hypertonus (contractions lasting > 2 minutes) in the presence of fetal heart rate abnormalities[16]
7. use of oxytocin infusion, at what cervix dilation started;
8. use of epidural anaesthesia, at what cervix dilation placed;
9. chorioamnionitis;
    a. defined clinically as fever during labour with maternal or fetal tachycardia and received broad spectrum IV antibiotics;

10. antepartum haemorrhage after start of IOL, cause (placenta abruption, other), timing (during IOL, during labour, during birth), associated with fetal and/or maternal complications;
11. uterine rupture;
    a. defined as clinically significant rupture involving the full thickness of the uterine wall and requiring surgical repair[20]
12. cord prolapse;
    a. occurs when the umbilical cord comes out of the uterus with or before the presenting part of the fetus
13. non-cephalic presentation, e.g. breech;
14. scalp lactate or pH performed during labour, results;
15. mode of birth (spontaneous vaginal, instrumental vaginal, caesarean);
16. vaginal birth within 24 hours of start of induction;
17. if instrumental delivery, then primary reason;
    a. reasons include: fetal distress, arrest of descent, maternal request, maternal distress
    b. if more than one reason, then clinician needs to determine which is the primary reason (usually fetal concerns would be prioritised)
18. if caesarean delivery, then primary reason and at what cervix dilation;
    a. reasons include: failed induction < 4cm no fetal concerns, failure to progress in established labour, fetal concerns, maternal request
    b. if fetal concerns and failure to progress together, then clinician needs to determine which is the primary reason (usually fetal concerns would be prioritised)
19. post-partum haemorrhage within 24 hours of birth, red blood cell transfusion, return to operating theatre for management;
    a. categorised as estimated blood loss 500-1000, 1001-1500, > 1500mL
20. post-partum endometritis;
    a. defined clinically as fever, fundal tenderness or purulent lochia and received broad spectrum IV antibiotics
21. admission to intensive care unit or equivalent;
22. post-natal satisfaction, assessed by questionnaire;

Fetal and neonatal:

1. Live birth;
2. Sex;
3. Apgar score at 5 minutes;
4. Birthweight, grams;
5. Abnormal arterial cord gas pH<=7.0 and/or base excess <=-12, and/or lactate>=6;
6. Birth injury;
    a. defined as: severe bruising, nerve trauma, or fracture
7. Admission to neonatal intensive care unit (NICU)/special care baby unit (SCBU); respiratory support (ventilation, CPAP, HHHF); mechanical ventilation (CMV or HFOV) and duration;
8. Infection, either culture proven, or suspected on clinical grounds with supporting lab evidence such as raised white blood cell count or C-reactive protein;
9. Seizures;
10. Neonatal encephalopathy, moderate or severe, and if due to Hypoxemic Ischemic Encephalopathy
11. Early neonatal death

Hospital:

1. Staff satisfaction, assessed by questionnaire;
2. Maternal length of stay;
3. Neonatal length of stay;
4. Pharmaceutical, equipment and consumable costs;
5. Health care utilisation costs;
6. Incremental cost effective ratio for caesarean rate.

15. Statistical analyses

15.1 Outcome evaluation:

Baseline demographic and clinical characteristics of each study group will be described. Analyses will follow the principle of intention-to-treat. Participants will be analysed according to the assigned treatment group at randomisation. Multivariable models will control for potentially confounding variables and include hospital site. Binary endpoints will be analysed using logistic regression to estimate odds ratios for the intervention. Continuous outcomes will be modelled using generalised linear models to estimate any changes in outcomes with the intervention compared to the control group. A p value of 0.05 will be considered to be statistically significant. We recognise there are a number of secondary outcomes; most will be correlated and thus we plan to report p values for these outcomes without corrections, which would be overly conservative. This analysis will be led by research team member A/Prof John Thompson, who is an Epidemiologist in the Department of Obstetrics and Gynaecology, School of Medicine, University of Auckland.

15.2 Economic evaluation:

Our approach will be to relate costs to outcomes for both arms of the study, allowing for the calculation of incremental cost-effectiveness ratios for the primary study outcome – caesarean delivery. In addition, a comparative cost analysis will be conducted to demonstrate the budget impact of wide-scale uptake of the intervention, given that length of stay and complication rates are higher for caesarean. The approach taken will be to monitor costs as captured through utilisation for mothers and their babies from the point when IOL is initiated until discharge from hospital. Costs will be calculated using Ministry of Health cost weights per event data which will allow for a summative total cost per delivery. Average costs will be compared between the study groups which will allow for the calculation of the net cost of the intervention. The net cost will be related to the primary outcomes of interest which will be then used to calculate incremental cost effective ratios (ICERs) for vaginal births and caesarean deliveries. This evaluation will be led by research team member Dr Richard Audas, who is a Health Economist and a Senior Research Fellow in the Department of Women's and Children's Health, Dunedin School of Medicine, University of Otago.

16. Monitoring of study progress

Progress reports will be circulated to all local investigators on a regular basis by the Auckland research team. Reports will include information such as number of women recruited, number of women completing the study, and any AEs or SAEs. Local investigators may be requested to provide updates on study activity at their centres throughout the trial.

17. Study timeline

2017
Protocol preparation, CRF preparation, randomisation program, REDCap database development, recruitment of OBLIGE Study midwife, study promotion.
Launch of Auckland recruitment: 26 October.
Locality approvals from all other research sites, contracts with Auckland DHB Research Office.
2018
Launch of recruitment for all other research sites. Recruitment completed by December 2019.
2020
Completion of data collection and data analysis. Publication preparation and submission.

18. Ethics and Regulatory

The study will be conducted in line with the Principles of the Declaration of Helsinki (1996) and the Note for Guidance on Good Clinical Practice CPMP/ICH/135/95) issued by the European Medicines Agency based on the International Committee for Harmonisation document E6, as well as any other good clinical practice standard which applies in NZ.

This trial received ethics approval through the Health and Disability Ethics Committee (HDEC) NZ full review pathway on 23 November 2016 (16/CEN/121).

19. Funding and Registration

Funding: Funding has been granted by the Health Research Council (HRC) of New Zealand (16/807) on 12 April 2017, and by A+ Trust (6907-PG-1604-003) on 7 July 2017.

Registration: This trial was registered with the Australia New Zealand Clinical Trials Registry (ANZCTR) on 6 June 2016 (ACTRN12616000739415).

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Appendix 1 – Schedule of assessments and procedures for randomised participants

	Enrolment	**Allocation**	**Study period**				
TIMEPOINT	***Up to 7 days in advance***	**0**	***< 1 hour***	***< 48 hours***	***At birth***	***Before hospital discharge***	***< 8 weeks after birth***
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Eligibility confirmation	X						
Baseline data collection	X						
Randomisation		X					
INTERVENTIONS:							
Balloon placement then home			X				
Vaginal PG gel placement			X				
ASSESSMENTS:							
Baseline variables: height, weight, primary reason for induction, initial bishop score, pain score during placement of balloon/PG gel			X				
Duration of balloon in situ, number of gels, second induction method, uterine hyperstimulation, rupture of membranes				X			
Oxytocin, epidural, chorioamnionitis, antepartum haemorrhage, scalp lactate, uterine hyperstimulation, uterine rupture, cord prolapse, non-cephalic presentation, mode of birth, vaginal birth within 24 hours, failed induction, stillbirth					X		
Gender, birthweight, Apgar < 7 at 5 mins, birth injury, abnormal arterial cord lactate					X		
Postpartum haemorrhage, endometritis, admit to Intensive Care Unit						X	
Neonatal infection, seizures, admit to NICU, neonatal encephalopathy, early neonatal death						X	
Maternal satisfaction							X

Appendix 2

Outpatient Balloon vs. Inpatient Gel

Oblige

This leaflet is for women who are having the first part of their induction of labour at home with a balloon. The soft flexible balloon has been filled with about three tablespoons of sterile water and placed just above the cervix (neck of the womb). You should not really feel it.

It takes about 18-24 hours for the cervix to be ready for labour. During this time, you can walk, pass urine, rest, sleep, shower, eat and drink normally. It would be unlikely for labour to start whilst at home or for the balloon to fall out.

Please watch for the following symptoms:

- Your membranes rupture. This is also called “water breaking.” For some women, they feel a ‘pop’ and a gush of fluid. For others, there is a continuous trickle or leak of fluid.
- Your labour pains start. For some women, they feel strong, regular, painful contractions right away. For others, it is more gradual.
- You don’t feel the baby moving normally.
- You have bright red bleeding from the vagina.

The first thing to do if you think any of these things have happened is to **ring the Hospital Midwife.** The number is:

_____

Ask to speak to a midwife and tell her that you are participating in the *OBLIGE Study*.

The midwife will:

- Ask you questions about how much fluid is leaking and the colour, and ask you to wear a pad
- Ask you questions about the labour pains
- Ask you questions about the baby's movements
- Answer your questions and make a plan

If your waters have broken, or **you have strong regular labour pains or contractions**, or **you don't feel your baby moving normally**, or **you have bleeding from the vagina**, you should come back to the hospital earlier than planned.

If the balloon falls out, no worries, get some sleep and return to the hospital in the morning as planned.

If all is going well at home, please return to the hospital tomorrow morning at _____. When you return, please let us know that you are participating in the *OBLIGE Study*. A hospital midwife will then assess you and the baby, and gently remove the balloon. Then we can continue your induction of labour.

THE UNIVERSITY OF AUCKLAND
NEW ZEALAND
Te Whare Wānanga o Tāmaki Makaurau