**Mi**fepristone versus placebo to increase the rate of spontaneous **labour** in people with a prior caesarean: A double blind randomised controlled **trial**

**(Mi-labourTrial)**

Protocol

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Table of contents

 Page

List of abbreviations

1. Summary 3
2. Background 3
3. Hypothesis and Aims 5
4. Safety 5
5. Study Design 6
6. Study Population 6
7. Study Numbers 8
8. Participant Selection and Recruitment 9
9. Study procedures and participant flow chart 10
10. Confidentiality and Data Collection 14
11. Interpretation, Generalizability and Overall evidence 17
12. Study timeline 17
13. Ethics and Regulatory 18
14. Funding and Registration 18
15. References 19
16. **Summary**

We intend to study the efficacy and safety of Mifepristone to increase the rate of spontaneous labour in people who have undergone a prior caesarean birth. People who plan a Vaginal Birth After Caesarean (VBAC) ideally await spontaneous labour. Induction of labour in this population increases the risk of repeat caesarean birth and the chance of complications, including uterine rupture. Lead maternity carers (LMCs) have limited options to offer people wishing for VBAC. Prostaglandin analogues, the most commonly used cervical ripening agents, are contraindicated in people with a prior caesarean. Oxytocin is an alternative. However, it requires an intravenous infusion, causes contractions and continuous cardiotogograph (CTG) monitoring is required when patients are receiving this medication. Oxytocin use is associated with a higher rate of unplanned repeat caesarean birth and labour complications including uterine rupture. Hence, avoiding oxytocin use is a priority. Mifepristone blocks progesterone receptors causing cervical softening without significant uterine contractions. This mimics the physiologic process people undergo prior to labour. We will assess the feasibility of using Mifepristone to increase the rate of spontaneous labour in people with a prior caesarean birth by performing a double blinded randomised controlled trial in which participants are allocated to receive either a single dose of mifepristone or a single dose of placebo.

1. **Background**

The aim of this study is to assess the feasibility of a novel use of the therapeutic agent, Mifepristone in people with term pregnancies who have undergone a previous caesarean birth and desire a vaginal birth. We will assess the rate of spontaneous labour within 48 hours between groups as our primary outcome. Spontaneous labour is an important factor for people with a prior caesarean. Entering labour spontaneously decreases the risk of repeat caesarean birth in this population, which has important respiratory and digestive implications for the baby 1 . Irrespective of eventual mode of birth, being exposed to labour also has other benefits including increased lung surfactant, increased lung-liquid absorption, increased perfusion of vital fetal organs and fetal metabolic effects 2. Babies born after experiencing labour are less likely to experience significant respiratory illness in the immediate neonatal period 3 .

Caesarean birth carries both short and long-term risks. Many people seek strategies to avoid a repeat caesarean and undergo a vaginal birth. In addition to the autonomous concerns of pregnant people, professional bodies worldwide, including the RANZCOG (Royal Australian and New Zealand College of Obstetricians and Gynaecologists) and the New Zealand College of Midwives (NZCOM) caution as to the risks of caesareans. Both RANZCOG and NZCOM are supportive of people choosing to attempt a VBAC under safe circumstances.

People who have undergone a caesarean birth are at an increased risk of requiring a repeat caesarean ranging from 25 to 50% 4 . Indeed the risk of a repeat caesarean increases after a person reaches 40 weeks of gestation. Requiring an induction of labour, especially after 40 weeks further increases the risk of a repeat caesarean birth. One contributing reason is the lack of options for cervical ripening to prepare the cervix for labour. Multiple studies using prostaglandin agents (including misoprostol) for induction of labour revealed an increased risk of uterine rupture with these medications **5-9**. This has left clinicians with mechanical methods such as the foley catheter or Cook double balloon catheter for cervical dilation and oxytocin infusions as the safe options for inducing labour in people desiring a vaginal birth after caesarean. There is ample evidence that people are more likely to give birth vaginally with a favorable cervical examination, especially if they have a history of caesarean birth **10,11**. The rates of vaginal birth are also higher in people who spontaneously labour. Additional methods to increase the chance of spontaneous labour are desirable to facilitate safe birth and to avoid labour induction in people with a history of caesarean.

Mifepristone is a progesterone antagonist. Mechanistic human and animal studies have found that Mifepristone occupies progesterone receptors and causes cervical ripening by decreasing cervical collagen organization 12,13. It is used for cervical ripening prior to pregnancy termination and has a favourable safety and side effect profile as compared to prostaglandin medications. Existing trials performed in Asia, Europe and the United States suggest safety in addition to an encouraging effect on cervical readiness for labour when given at term gestational ages 14-16. However in spite of this, the drug is not commonly used in the third trimester, because of the common use of prostaglandin agents in people without a uterine scar (dinoprostone and misoprostol), although these drugs are contraindicated in people who have a prior caesarean 5,6,8,9. Further trials are required to study the feasibility of Mifepristone to increase the rate of spontaneous labour in people with a previous caesarean.

The existing evidence for use of Mifepristone in the third trimester indicates safety and efficacy. In European trials, when used in outpatient regimens, Mifepristone has been found to be superior to placebo for cervical ripening and resultant initiation of spontaneous labour 17-19. Multiple dosing regimens have been assessed 20. Dosing above 200mg has not been associated with improved outcomes as far as success of cervical ripening or time to labor and giving birth is concerned 20. However, 200mg is superior for cervical preparation to the use of 50mg dosing for term gestational ages 21.

Trials from the United States using 200mg of Mifepristone have indicated that people with unfavourable cervical examinations treated with Mifepristone need less oxytocin and misoprostol when subsequently induced 22. Likewise, people with preterm premature rupture of membranes need lesser doses of oxytocin if treated with Mifepristone before oxytocin administration 23.

Previous work has focused on people with unfavorable cervical examinations, as this indicates the person has a lower chance of spontaneous labour than a person with a favourable cervical examination. When Mifepristone became popular in the 1990s, few people with a history of cesarean were included in studies, although one pilot randomizing 32 people to mifepristone or placebo indicated effectiveness and safety of mifepristone 19. Mifepristone use was associated with a lower need for other induction agents and there was no increased maternal or fetal risk 19. Importantly, most of the trial participants who received mifepristone went into spontaneous labour without the need for contractile agents, compared to only a few in the placebo group. There was also a larger trial with a subset of patients with a history of cesarean (n=52). There were three uterine ruptures which were not clearly documented (as ruptures or dehisences) and participants in this trial also received other contractile agents to effect birth. It is likely these participants with uterine rupture were receiving contractile agents (including now contraindicated prostaglandins) and supra-therapeutic dosages of Mifepristone 20. More recent data on Mifepristone in people with a prior caesarean birth exists which is reassuring in relation to risk profile. A recent pilot trial from India showed encouraging results for participants with a history of caesarean who were administered Mifepristone 24 . Though a small study with only 52 participants in total, the caesarean rate was lower in the Mifepristone group (20%) than the placebo group (40%) 24 . A further pilot trial randomized 36 people to each group and likewise showed a benefit to the use of Mifepristone prior to the use of a catheter for cervical ripening 25 . Though these pilot studies are small, they do provide safety data of import and pave the way for a larger trial.

Mifepristone does not appear to cause significant contractions in most people. Rather, it appears to initiate the body’s own hormonal cascade to allow for spontaneous labour, and likely increases sensitivity to exogenous contractile agents 26,27. Mifepristone is commonly used in patients with a history of caesarean birth for cervical preparation before second and third trimester termination of pregnancy in New Zealand. There is also data from medically induced abortions indicating safety of the drug in the setting of prior caesareans. One Western Australian study reported on 199 patients with a history of one or multiple caesareans, who were administered mifepristone as part of their abortion care in the second trimester 28 . There were no uterine ruptures in the group. Their interval to birth was also shorter than the group of patients who did not receive mifepristone and they required less contractile medication 28 . Again, this is particularly important with a uterine scar and provides important data as it relates to safety and efficacy.

We aim to perform a randomized controlled trial to assess whether Mifepristone increases the rate of spontaneous labour in people with a prior caesarean birth. We intend to recruit participants from two catchments within Auckland, Te Toka Tumai Auckland and Te Whatu Ora Counties Manukau.

1. **Hypothesis and Aims**

We hypothesize that the administration of a single 200mg oral dose of mifepristone will increase the rate of spontaneous onset of labour within 48 hours in pregnant people with a prior caesarean compared to placebo.

1. **Safety**

***Potential risks of Mifepristone/Placebo administration***

Drug Allergy – This is a rare event and we do not anticipate any participants to experience this complication. However, an allergy to any new substance can be encountered.

Uterine Rupture – This rare event can occur in any person who is laboring. It is more common in people attempting a vaginal birth after caesarean birth. The rate is expected to be approximately 1:200 people. We do not anticipate that the risk would be higher in people receiving Mifepristone. It is relevant that we hypothesize people who receive Mifepristone will be more likely to labour and hence less likely to require labour induction or augmentation with oxytocin; therefore the risk of uterine rupture may actually be expected to be lower in trial participants receiving Mifepristone.

1. **Study Design**

This is a double blinded, randomised controlled trial in which participants will be allocated either oral Mifepristone 200mg or a look-alike placebo.

***Recruitment:***

Participants will be recruited at presentation to the hospital or antenatal clinic for pregnancy care or via their Lead Maternity Carer. We will actively promote the trial within the midwifery community, within the obstetric provider community, via development of a trial website, promotion through our professional educational networks and via trial pamphlets provided to LMCs and posters and banners in antenatal clinics and on antenatal wards. Additionally, IOL and caesarean birth are usually requested 1-2 weeks ahead of time. When bookings are made we will create a tick box regarding the Mi-labour Trial to trigger discussion with potential participants at that point. People eligible for the trial may also be contacted via phone if that is the most convenient way for them to receive the information about the trial. Either the LMC or the research staff may contact potential participants by phone so that people may avoid travelling to an appointment to have a discussion and receive information about the trial. The Mi-labour Trial will be coordinated by the Principal Investigator (PI), the Co-Investigators and any staff employed either in whole or in part for the purposes of study completion.

1. **Study Population**

***Inclusion Criteria***

Pregnant people with a live singleton and cephalic presentation

History of one or two prior caesarean births

Intention to deliver vaginally

Intact membranes

Normal CTG prior to randomisation

Maternal age 16-50 years

Gestational age between 36 6/7 and 41 6/7 weeks gestation

***Exclusion Criteria***

History of classical caesarean birth or other major uterine surgery including transmural myomectomy

Fetal malpresentation or other contraindication to vaginal birth or induction of labour

Fetal growth restriction with Absent or Reverse End Diastolic Flow noted on umbilical artery Doppler

Rupture of amniotic membranes

Planned induction of labour or caesarean birth within the next 48 hours

*Trial participants:*

Eligible people will be in one of two groups: those without a medical indication for birth prior to 39 weeks, and those with a medical indication for induction of labour prior to 39 weeks.

* Potential participants without a medical indication for IOL until 41 weeks will be eligible to undergo study procedures between 38 weeks and 6 days and 41 weeks and 6 days.
* People who have an indication to give birth prior to 39 weeks are also eligible to participate in the trial.

If their birth is indicated from 37 weeks, the earliest study medication may be administered is 36 weeks 6 days.

If their birth is indicated from 38 weeks, the earliest study medication may be administered is 37 weeks and 6 days.

\*It is important to note that most studies indicate the minimum amount of time taken to see an effect of Mifepristone is approximately one day (24 hours). For this reason the medication may be administered a day prior to the date the participant would be eligible for induction. Many participants with inductions planned for 37 weeks would not have this until several days past this (for example 37 weeks 2 days).

\*The counseling we will provide as part of the trial is that we would not allow inclusion of people who have IOL or caesarean planned within the next 48 hours. Additionally, it would be best to give the medication the maximum time to work, so scheduling an induction or repeat caesarean 2-3 days after study drug is administered would likely give the best chance of drug effect (spontaneous labour and avoidance of labour induction) and would still be within guidelines. Participation in the study does not preclude later induction of labour, in which case the usual process would be followed (options including Foley catheter placement, amniotomy or oxytocin infusion) or later elective caesarean birth (in the case the participant has considered options and does not wish to have an induction with contractile agents because of the associated risks).

\*though potential participants may discuss the study with their LMC or an investigator and enroll to undergo study procedures earlier during the pregnancy, no study procedures will be undertaken before an appropriate gestational age has been reached as outlined above. The research midwife will confirm eligibility for the trial as well as an intention to birth in hospital with the participant and will also confirm that the trial entry is occurring at an appropriate gestational age.

***Participant withdrawal from study after randomisation***

Participants can choose to withdraw from the clinical study procedures at any time. In participants who withdraw but consent for their data to be retained, their data will be used as a part of the intention to treat analysis.

1. **Study Numbers**

***Sample size calculation***

Our primary outcome is spontaneous onset of labour within 48 hours of study drug administration. A power calculation has been performed based on existing effect sizes from trials 17,18 . Operating under the assumption that the spontaneous labour rate will increase from 10% to 30% in the group receiving Mifepristone with a power set at 90% and a two-sided confidence interval at 95%, a total of 168 participants will be required. We will stratify our randomization by gestational age (gestational age <38 weeks 6 days and gestational age ≥38 weeks 6 days) and by study site.

\*We intend to recruit up to 200 participants to allow for 1) withdrawals for use of data 2) randomization in participants who then choose not to participate and do not take the study drug 3) loss to follow up (in this situation a participant would seek care and give birth outside of the two study centres), 4) participants who begin labour after randomization but before they take the study drug, (which is possible but unlikely). We recognize that we may be able to cease recruitment at 168 participants as all four reasons for additional recruitment are unlikely.

***Feasibility***

Te Toka Tumai Auckland provides care for approximately 6,000 pregnant people per year.4 Te Whatu Ora Counties Manukau supports >7000 people in their births each year. In each hospital medically-indicated inductions are common, occurring in 25-35% of births at the study sites. Maternal diabetes is the leading indication for IOL. Additionally, many people without medical indication for early induction of labour plan vaginal birth after caesarean (VBAC) at both hospitals and wish to avoid continuing pregnancy to 41 weeks, at which time birth (via IOL or caesarean) is recommended.

While there are other Auckland research studies recruiting pregnant people at term who intend to birth vaginally, people with a history of caesarean are excluded, meaning that this research will not be in any direct competition. Additionally, if our hypothesis is correct, the treatment arm may result in a lower need for IOL and may actually take some pressure off the hospital service.

We will aim to recruit 2 participants per week. This will translate to 100 participants per year. Our projected recruitment is 2 years.

1. **Participant Selection and Recruitment**

Pregnant people with a history of caesarean birth who are eligible for a vaginal birth after caesarean (VBAC) will be approached for inclusion in this study after a discussion with their LMC. They will undergo an interview with the investigator or the research midwife either in person or via phone. The potential participant will be provided with a Participant Information Sheet and Consent Form. They will be given time to read this form in full and discuss it with their LMC and whanau as needed. Contact information for the research team will be provided. The study can be discussed at any timepoint but participants will not undergo study procedures until they are at the prespecified gestational ages (above). They will be scheduled for an appointment with the research midwife to sign the consent document (if this has not been done prior) and to undergo study procedures. Study procedures will be carried out at the location of the patient’s choice. If potential participants have an appointment with their LMC or a hospital clinic, the research midwife can meet them at that location. Alternatively, the research midwife can perform a home visit or make a visit appointment at one of the clinical sites for the sole purpose of enrolling in the study. At the first study visit, the participant will be provided with an information sheet regarding symptoms that should result in assessment for labour. With participant consent, the LMC will be contacted with information regarding clinical progress towards labour on the second study visit. Participants will likewise be encouraged to seek labour assessment should they start contracting at any time after participation in the study. The risk sheet will be updated by the study team in indicate that the participant has been enrolled and ingested study medication. The risk sheet will also indicate that people should be encouraged to come in early with any labour symptoms.

The signed consent form will be kept with the other data collection forms and hard copies stored securely. The data from these documents will be entered into an online, password protected spreadsheet under the participant’s study number, a copy of the consent form put into the participants’s notes, and another copy provided to them.

The participant will have pertinent clinical information recorded (this is specified below).

***Screening log***

The researchers will keep track of all potential participants, all potential participants who are approached for inclusion in the study who accept participation as well as those who decline. A record will be kept of all people who chose to participate and those who declined. Demographic data only will be collated on people who are approached but decline to participate in order to assess whether we recruit a representative sample of the people eligible to participate.

***Randomisation***

Web-based randomisation will be performed 27. Centralised online randomisation will occur via liggins trials.

Randomisation site

<https://www.ligginstrials.org>

Site access: To be provided by the Clinical Data Research Hub/Maternal and Perinatal Central Coordinating Research Hub (CCRH) after database implementation

Summary View (Admin): To be provided by the Maternal and Perinatal Central Coordinating Research Hub (CCRH) after database implementation

The randomisation schedule will be prepared in advance and stratified for: Gestational age < 38 weeks 6 days versus gestational age ≥ 38 weeks 6 days and study site.

Allocation is in a 1:1 ratio to oral Mifepristone or oral placebo. The randomisation process will assign each participant with a unique Study ID Number. If a participant is found not to be eligible for the study when their details are entered into the randomisation program, the program will return a screen failure notification.

***Treatment groups***

Participants will be randomised to one of two groups

1. Oral Mifepristone
* Medication provided and ingestion observed.
1. Oral Placebo
* Medication provided and ingestion observed.

***Blinding***

Mifepristone is dispensed as small white tablets. We will utilize a compounding service to produce a look-alike placebo for use in this study. Study tablets (both mifepristone and placebo) will be placed inside identical capsules.

The identical-appearing capsules will be stored in identical bottles labelled with numbers. When the data on a participant is entered into the online randomization system, including the stratification information, the system will allocate a bottle number to be opened and administered to the participant. The research midwife will have access to the bottles and will remove the numbered bottles as allocated by the online randomization system.

We will utilize staff at the Te Toka Tumai Auckland research pharmacy to prepare the medications and label the bottles so no staff connected to the study will know which numbered bottles contain Mifepristone and which contain placebo.

The research midwife will dispense a single study dosage from a single bottle in accordance with the instruction from the randomization website and record observing the participant ingest the study medication. This bottle will then be discarded. There will not be a way for the participant, research midwife, or the investigators to identify which arm of the trial the participant is in due to this process. Unblinding will not occur until after recruitment and data analysis is complete, at which time, the Clinical Data Research Hub will unblind the allocations for the entire cohort of participants.

1. **Study procedures**

***Individual participant study flow chart***

Person is identified as eligible

↓

Discussion regarding study with clinician or member of the research team

(after discussion with LMC)

Participant Information Sheet and Consent Form provided

↓

Informed consent not obtained: Entered into screening log and demographic data recorded (end of participant flow for eligible people who decline)

Informed consent obtained: Entered into participant log and demographic data recorded

↓

CTG performed

Baseline cervical Examination performed (participant may decline if they prefer not to have a cervical examination)

↓

Randomisation

Study drug ingestion observed

Participant advised to attend assessment unit if appears to be in early labour

Information provided to participant and LMC regarding seeking labour assessment

All participants who are randomized will be analyzed as intention to treat

↓

Baseline Data Collection

↓

Participant seen in 24 hours for planned appointment

CTG performed

Cervical examination performed (participant may decline if they prefer not to have a cervical examination)

Participant advised to attend assessment unit if appears to be in early labour

LMC contacted with any concerns for early labour

↓

Participant returns to usual prenatal care

↓

Data collection about labour and birth, maternal outcomes,

laboratory values, pathology results

 and neonatal outcomes to discharge from hospital

Participant survey during postpartum via phone

***Baseline data collection***

Participants in the Mi-labour Trial will have baseline data collection performed. This will be via chart review. Data collection will include: Maternal age, maternal ethnicity, type of LMC, booking height, booking weight, prior indication for first prior caesarean birth, initial Bishop (cervical assessment) Score, prior vaginal birth, gestational age, primary indication for IOL, hospital site

***Labour Outcomes data collection***

Data collection will include: Induction of labour and indication for induction, caesarean birth and indication for caesarean, Cervical examination findings (all cervical examinations), total number of cervical examinations, cervical examination at the time of Artificial Rupture of Membranes (ARM), time of ARM, time of spontaneous rupture of membranes (SROM) if this occurs, birth with intact membranes if this occurs, time to vaginal birth, time to caesarean, indication for caesarean birth, any complication of either vaginal or caesarean birth, use of and indication for use of forceps or ventouse for birth, estimated blood loss intrapartum and postpartum, neonatal weight, neonatal Apgar Score at 1 and 5 minutes, time of epidural anesthesia administration, need for entonox for pain relief in labour, need for narcotic medication for pain relief in labour, fetal scalp lactate sampling performed in labour and results, use of oxytocin to augment or induce labour, maximum oxytocin infusion rate (milliunits/minute), whether oxytocin was turned off, or down, tachysystole/hyperstimulation/hypertonus, administration of a tocolytic during labour, performance of cord blood pH, lactate and base excess and results if they were performed.

***Management of labour***

Participants in the trial will have their labour managed per the clinical decisions made by their LMC or the hospital obstetricians.

Routine intrapartum care:

Oxytocin – If oxytocin is needed, this will be administered after discussion with the participant. A low-dose protocol is used at both institutions. Low-dose begins with 1-2mU/min increased incrementally by 1-2 mU/min at 30 min intervals.

The Intrapartum Fetal Surveillance Clinical Guideline should be followed for the management of fetal heart rate abnormalities, as would usually occur in the clinical care of laboring participants.

Cord lactate and/or gases will be taken as indicated for clinical reasons on participants in this trial.

***Post-study survey***

A brief survey will be provided to participants to complete regarding their experience of study participation, labour and birth. This will be completed via phone and will be done within 12 weeks of giving birth.

***Safety Assessment and Monitoring***

***Severe Adverse Events (SAEs)***

Antepartum haemorrhage (defined as >500mL blood loss intrapartum)

Maternal adverse events that require unexpected hospitalization (this excludes normal presentation for labour care)

Maternal birth injury, surgical (need for hysterectomy)

Blood transfusion of 4 or more units of PRBCs

-Maternal admission to intensive care unit or equivalent

Maternal death

Stillbirth

Neonatal death, early

Neonatal encephalopathy (moderate or severe, as determined by the treating team)

-Cord prolapse

Neonatal birth trauma (neonatal fracture, intracranial haemorrhage, nerve palsy, spinal injury)

-Uterine rupture

***Adverse Events (AEs):***

Routine data collection will include all AEs that occur from the time of randomisation until maternal discharge from hospital and neonatal discharge from hospital after birth.

In all people planning to give birth, there is some risk involved. That is to say, giving birth is not without the possibility of a poor outcome. Expectant management, IOL and caesarean birth all have risks. We do not anticipate that being involved in the Mi-labour Trial would increase any physical risks to participants. Though, we do hypothesize that the arm the receives the Mifepristone will have a higher rate of spontaneous labour. The underlying risks of labour will be collected, and include:

* Chorioamnionitis in labour (defined as maternal fever >37.5 degrees Celsius on 2 occasions, or ≥ 38 degrees Celsius on one occasion, in labour and one other clinical symptom or sign, or maternal fever and decision to treat empirically)
* Isolated maternal fever >37.5 degrees Celsius or ≥ 38 degrees celsius in labour without the diagnosis of chorioamnionitis
* Postpartum haemorrhage (defined as >500mL blood loss postpartum)
* Postpartum endometritis (defined as maternal fever ≥ 38 degrees Celsius and hospitalization for intravenous antibiotics, within 7 days of giving birth)
* Maternal birth injury (severe perineal laceration, complicated repeat caesarean birth defined as uterine extensions)
* Neonatal birth injury (neonatal birth trauma from caesarean or vaginal birth, neonatal seizuresnot due to hypoxic ischaemic encephalopathy)

***Investigator review of AEs/SAEs***

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

* Duration: when 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: details will be provided as relevant to the AE/SAE

***Procedure for AE/SAE reporting***

The PI must be informed of any SAE within 48 hours of the occurrence by either phone or email. The SAE report can be completed in hard copy, scanned and emailed to meghan.hill@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. In such a case, the Chair of the DSMC may request that the study allocation be revealed to them alone (The PI will not be informed unless the Chair decides to inform them) in order to better inform decision making. AEs will be compiled by the PI and written into a report on a six-monthly basis. This will be provided to the DSMC.

 All adverse events must also be documented in the participant’s notes.

PI contact details: Dr. Meghan Hill, 027 309 5220 meghan.hill@auckland.ac.nz

***Data safety and Monitoring Committee (DSMC)***

The DSMC for the Mi-labour Trial will require a minimum of two members. There will be a chair and a minimum of one additional member. The DSMC receives reports from the PI every 25% of recruitment reports back to the PI within three months of receiving the reports. The DSMC will receive information of trial recruitment, study withdrawals and serious adverse outcomes.

1. **Confidentiality and Data Collection**

Randomisation will be performed through the Liggins Trial Randomisation site. Each participant will be entered electronically into this system. This information will the be imported into the secure REDCap data system.

Data will be collected on all enrolled participants as specified above. Data will be entered into a REDCap database developed for the Mi-labour Trial by the research team. The REDCap database will be stored on the Te Toka Tumai Auckland secure server with restricted access. Data entered into the Database will be linked to the study number only.

All hard copy study materials that contain the participant’s identifying information including the consent forms will be stored for a minimum of 26 years at the Department of Obstetrics and Gynaecology, University of Auckland, under the responsibility of the PI.

**Outcome Measures**

***Primary Outcome***

Spontaneous onset of labour, defined as regular uterine contractions causing cervical change (with a minimum cervical dilation of 3cm).

**Secondary Outcomes**

***Maternal***

To assess other outcomes in participants provided with mifepristone as opposed to placebo:

Rate of rupture of membranes at term prior to labour, measured within 48 hours of drug ingestion

Rate of rupture of membranes at term prior to labour where induction of labour is performed, measured until birth (not more than 30 days from drug ingestion)

Rate of rupture of membranes at term prior to labour where a prelabour caesarean is performed (rather than induction with oxytocin infusion), measured until birth (not more than 30 days from drug ingestion)

Rate of induction of labour

 Rate of induction of labour with Foley catheter (as initial approach)

 Rate of induction of labour with amniotomy (as initial approach)

Rate of induction of labour with exogenous contractile agent (oxytocin, as initial approach)

Rate of induction of labour with exogenous contractile agent (oxytocin, as sequential approach)

Rate of caesarean birth

Rate of caesarean birth for any indication (overall rate)

Rate of caesarean birth for fetal heart rate abnormalities (as identified from operative report)

Rate of caesarean birth for labour dystocia (as identified from operative report)

 Rate of fetal heart rate abnormalities

Rate of fetal heart rate abnormalities resulting in fetal scalp lactate sampling

Rate of fetal heart rate abnormalities resulting in instrumental vaginal birth (as listed on delivery report)

 Rate of infants born with 5 minute Apgar Scores <7

 Average time to vaginal birth from onset of labour

Cost effectiveness (calculated by assessing cost of induction, caesarean and delivery unit stays in days for each participant)

 Time to ARM (artificial rupture of membranes)

Uterine tachysystole (defined as > 5 contractions per 10 minute period for at least 20 minutes)

Uterine hyperstimulation(defined as > 5 contractions per 10 minute period for at least 20 minutes with concurrent abnormal fetal heart rate pattern)

Average time from mifepristone administration to onset of labour

Average time from mifepristone administration to vaginal birth

 Use of epidural anesthesia, time placed

 Use of intravenous narcotic analgesia

 Antepartum haemorrhage (defined as 500mL), timing, amount, treatment

 Intrapartum haemorrhage (defined as 500mL), timing, amount, treatment

Postpartum haemorrhage (within 24 hours of birth, defined as 500mL), timing, amount, treatment

 Uterine rupture

 Cord prolapse

 Non-cephalic presentation (breech, transverse, oblique), treatment, outcome

 Admission to the ICU or equivalent

Maternal satisfaction, based on survey data collected after birth

***Fetal and neonatal***

Live birth

 Sex

 Apgar score at 1, 5, 10 minutes (if applicable)

 Birth weight

 Arterial and venous cord blood gases, lactates, base excesses if collected

Abnormal arterial cord blood pH (≤7.10) or lactate (≥4.0)

 Admission to the Neonatal Intensive Care Unit (NICU)

 Seizures

 Neonatal encephalopathy (defined as moderate or severe)

 Neonatal death (early)

***Hospital***

Cost effectiveness (calculated by maternal length of stay during birth admission and any readmission within 7 days of birth, neonatal length of stay during birth admission, use of operating theatre)

***Statistical analysis***

***Outcome evaluation***

A formal statistical analysis plan (SAP) will be completed and uploaded to the trial registration site.

STATA Statistical software will be utilized to perform statistical calculations.

Descriptive data will be presented on the study groups.

Analyses will follow the principle of intention-to-treat. All primary and secondary analyses as listed in the SAP will be reported.

The statistical analysis will be undertaken blind to allocation.

Multivariable logistic regression modeling will be used to adjust for the stratification variables (gestation at randomisation and site of randomisation) in analysis of the primary outcome.

Stratified analysis will also be undertaken by the stratification variables gestation at randomization and site.

Binary endpoints will be analysed utilizing chi squared analysis. Continuous outcomes will be analysed by linear and time series analyses as appropriate (e.g. linear regression or GLM and Sign rank or Cox Proportion Hazard models (time to vaginal birth, for example).

A p value of 0.05 will be considered statistically significant. There are multiple secondary outcomes. These will be reported with p values. No adjustment is planned for multiple tests.

Any exploratory analyses (post-hoc analyses) will be specified as such when they are reported.

There is an experienced epidemiologist (LS) with a background in obstetric research within the department of Obstetrics and Gynaecology. Statistical calculations will be performed by this investigator in their role at Te Toka Tumai Auckland. Support will be accessed as needed from a statistician within the Department of Obstetrics and Gynaeology.

Reports will be prepared for the DSMC by the PI. The PI will prepare components of the reports relating to recruitment targets, protocol violations, SAEs and other components of the study. The exception is the statistical reports provided on outcome data to the DSMC. This portion of the report will be provided separately by the epidemiologist co-investigator (LS). This co-investigator may access support from a statistician to aid in preparation of these reports, if needed. The outcome data will not be provided to the PI, or the rest of the study team, unless recommended by the DSMC.

1. **Interpretation, Generalisability and Overall evidence**

Following completion of the study, full results will be discussed by the investigators and the group will assess any potential bias that has been introduced during the study period. The study groups will be compared (for demographic information only) to those who declined participation to assess whether or not the study has included a representative sample of people desiring to have a vaginal birth after caesarean. The investigators note that New Zealand is a multiethnic society and believe this to be a strength of the study, lending the results to external validity. The findings of the study will be compared to what is already known regarding the use of Mifepristone in people with a prior caesarean birth. Ideally results of the study will indicate whether or not there appears to be utility in adopting the use of Mifepristone in people with a prior caesarean in routine clinical practice.

1. **Study timeline**

***2023***

Protocol preparation, CRF preparation, Participant information sheet and consent form preparation, Secure database development

***2024***

Launch recruitment April 2024

***2025***

Completion of data collection and analysis.

Presentation of findings at conference. Intended conference: Society for Maternal-Fetal Medicine Annual Meeting

Publication preparation and submission.

1. **Ethics and Regulatory**

This study will be submitted for approval through the Health and Disability Ethics Committee (HDEC) NZ full review pathway between April 2023 and September 2024. The study will be submitted for locality approval through the Te Toka Tumai Auckland and through the Te Whatu Ora Counties Manukau Research Offices on the same timeline.

1. **Funding and Registration**

***Funding***

This study is not currently funded. Recruitment and coverage of trial-related costs will not be feasible until funding is obtained. Having ethical approval in place will make obtaining funding easier. We intend to secure funding for independent preparation of study drug for the trial, employment of a research midwife to assist with recruitment, data collection and collation, publication fees and ongoing promotion of the trial.

***Registration***

This trial will be registered with the Australia New Zealand Clinical Trials Registry (ANZCTR) prior to trial commencement.

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