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A Double-Blind Randomised Placebo Controlled Trial of Melatonin as an adjuvant agent in Induction of Labour (MILO): Study Protocol

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Abstract:

Introduction: Induction of labour is a common practice. The aim of induction of labour, beyond a healthy mother and baby, is the desire to achieve a vaginal birth. However, in Australia up to 40% of women undergoing labour induction will ultimately have a caesarean section. As a biological role for melatonin in the onset and progress of labour has been demonstrated, we aim to test the hypothesis that addition of Melatonin will reduce the need for caesarean section.

Methods and analysis: This is a double blind randomised, placebo-controlled trial in women undergoing induction of labour at term. We plan to randomise 722 women (1:1 ratio) to receive either Melatonin (four doses of 10 mg Melatonin: 1st dose – at the time of cervical balloon insertion, 2nd dose – at time of oxytocin infusing commencement, 3rd dose- 6 hours after the second dose, 4th dose- 6hours after the 3rd dose) or Placebo (same dosing regime). Administration of the intervention will cease as soon as the baby has been born. The primary outcome measure will be caesarean section. Secondary outcomes will include duration of each stage of labour and time from induction to birth, total dose of oxytocin administration, epidural rate, indication for caesarean section, rate of instrumental deliveries, birth within 24 hours of induction commencement, estimated blood loss, Apgar score at 5 minutes, NICU admissions and participant satisfaction. Maternal melatonin levels will be measured immediately before administration of second dose of the trial intervention and 3 hours after the commencement of the oxytocin intravenous infusion and at the time of birth in order to determine any differences.

Conclusion: This study will show if the addition of Melatonin in women in whom labour is induced will improve labour outcomes.

Ethics and dissemination: The study is conducted in accordance with the conditions of Monash Health HREC (RES -17-0000-168A). Findings from the trial will be disseminated through peer-

reviewed publications and conference presentations. Trial registration number: ACTRN12616000311459, Universal trial number: (UTN) U1111-1195-3515. Trial Funding: NHMRC Project Grant APP1123498

KEYWORDS: Melatonin, Induction of Labour, Caesarean

Strengths and limitations of the study:

- This is the first randomised placebo controlled trial designed to study the effect of melatonin in reducing caesarean section rates
- Both participants and clinicians providing intrapartum care will be blinded to the trial intervention allocation, thus decisions regarding the need for a caesarean section cannot be influenced by the allocation.
- A potential limitation of this study is it is conducted at a single health service.

Introduction:

Induction of labour (IOL) is one of the most common obstetric interventions. In Australia, the labours of 31% of women are induced, up from 25% only a decade earlier [1]. IOL is principally performed with the intent of reducing risks to the mother and/or baby by simply calling an end to the pregnancy. The ultimate goal of IOL is to achieve a vaginal birth with no maternal or infant morbidity. However, despite randomised controlled trials indicating that IOL does not increase caesarean section rates [2, 3] outside the tight confines of trials the reality for women globally is that up to ~40% of women having their labours induced require a caesarean section, this is particularly true if they are nulliparous [4-8].

Failure of IOL resulting in a caesarean section is important for a number of reasons. Firstly, it may be associated with disappointment for the woman. There are also well established links between labour complications, including the need for a caesarean birth, and the risk of postnatal depression[9], particularly in first time mothers[10]. Women who require a caesarean section are also less likely to breastfeed their baby [11, 12]. An intrapartum caesarean is associated with greater maternal morbidity than vaginal birth, including higher rates of postpartum haemorrhage, endometritis, venous thromboembolism, a longer recovery time and an increased rate of hospital readmission [13, 14]. Having a caesarean section is also associated with an increased risk of morbidities in subsequent pregnancies including preterm birth, abnormal placentation and uterine rupture [15, 16]. Improving the success of IOL is therefore important not only for the current labour, but all future pregnancies too.

It is most common practice for the induction of labour process to begin in the morning. Optimum staffing levels are considered the main driver for this [17]. However, such timing may not be optimal for the woman. First formally reported over 60 years ago, was the observation that

spontaneous labour most commonly starts at night [18]. In a study of 19,000 labours the peak time of onset was between 2am and 3am [18]. More interestingly, labours commencing between 11pm and 1 am were significantly shorter than those that commenced between 4am and 7pm [18]. Over the years these intriguing observations have been confirmed by others (reviewed in [19]). The accepted explanation underlying the observations has been that uterine muscle (myometrial) fibres are more sensitive to the effects of endogenous oxytocin at night [20, 21]. The reason for this increased sensitivity at night is thought to be due to melatonin.

Melatonin (5-methoxy-N-acetyltryptamine) is an endogenous hormone produced primarily by the pineal gland. It provides circadian and seasonal timing cues [22]. In adults, melatonin levels remain low throughout the day. In the early evening the levels begin to increase peaking between 2am and 3am at night and then falling back down to low daylight concentrations again in the morning[23]. This circadian rhythm of melatonin is amplified in pregnancy. In particular, healthy pregnant women have higher concentrations of melatonin both at night and during the day compared to non-pregnant women [24] most likely due to *de novo* placental synthesis [25]. In addition, maternal melatonin levels increase with advancing gestation peaking during labour and then falling rapidly after birth (reviewed in [25]). The myometrium (uterine muscle) expresses the melatonin receptor MT2 and it is more highly expressed in labouring myometrium, collected at intrapartum caesarean section, than in myometrium from non-labouring women [26]. Melatonin also increases the sensitivity of the myometrium to oxytocin-induced contractions [27]. Co-treatment of an immortalised myometrial cell line with melatonin and oxytocin resulted in a 2-fold increase in contractile response compared to oxytocin alone [27]. In these same studies melatonin was also shown to increase the expression of the protein connexin 43, a gap-junction protein necessary for myometrial cell communication and the synchronization of uterine

contractions[27]. Taken together, these *in vivo* and *in vitro* observations suggest that melatonin plays a biological role in the timing of onset of spontaneous labour, and in the effectiveness of spontaneous uterine contractions in labour. As IOL with an oxytocin intravenous infusion normally occurs during the daytime, women do not experience the physiological increases in melatonin that occur prior to going into spontaneous labour at night, we hypothesise that administering melatonin at the time the induction process commences will reduce the IOL failure rate.

We will undertake a double blind randomised placebo-controlled trial of oral melatonin administration at induction of labour to reduce caesarean section rates in healthy women with a singleton pregnancy at full term.

Methods and analysis:

This protocol has been designed in accordance with the SPIRIT 2013 Guidelines.

Study Design: Phase III double blind, randomised, placebo controlled trial.

Study setting: Participants will be recruited at Monash Health, Monash Medical Centre, a level six university affiliated teaching hospital in metropolitan Melbourne, that provides care for up to 9,000 women a year.

Subjects: Women with a singleton pregnancy who are undergoing induction of labour.

Inclusion criteria:

- ≥ 18 years and < 50 years of age
- Nulliparous or multiparous (para 1-3) women with a singleton pregnancy in cephalic presentation
- Full term (≥37 weeks)
- Bishop's score < 5 (a strongest predictor of failure of induction) [28]
- Intact membranes
- Method of induction includes the use of cervical balloon catheter or prostaglandin (gel/tablets/pessary)
- No known significant maternal or obstetric medical condition that would affect melatonin pharmacokinetics or maternal safety

The specific exclusion criteria are:

- Fetal growth restriction (FGR) < 10th centile with Doppler changes
- Any known congenital anomaly of the fetus

- Any known abnormal karyotype of the fetus
- Non-reassuring fetal status
- Not willing to or inability to follow the procedures outlined in participant information and consent form
- Known allergy or sensitivity to melatonin and its formulation
- Mentally or legally incapacitated or not able to provide informed consent
- Participation in another trial where there is pharmaceutical or any other nutritional intervention

Participant recruitment and informed consent

Potential participants will be identified and recruited from the obstetric departments. A researcher, not involved in the provision of clinical care will approach the woman and provide the Participant Information and Consent Form. The researcher will provide a verbal explanation of the trial, including a description of the trial processes, the voluntary nature of the trial and that a decision to participate, or not, will not affect their clinical care. The woman will be encouraged to discuss their participation with others of their choosing and given sufficient time to consider if they wish to take part, or not. If the woman agrees she will sign the participant information and consent form.

Randomization and blinding

A perinatal epidemiologist not be involved in the trial will prepare the randomization sequence. Randomisation will occur on a 1:1 ratio of melatonin to placebo. Both the melatonin and placebo tablets will be indistinguishable and contained in pre -prepared bottles by the pharmacist at Monash Health. The researcher, clinical staff or the participants will know whether melatonin or

placebo tablets have been administered. At the time of recruitment, each participant will be de-identified and assigned a unique trial code. Subsequently, all data and tissue samples collected from the participant will be stored only labelled with this associated code.

Study intervention

Participants will be given either melatonin 10mg (Circadin® prolonged release melatonin, manufactured by Aspen Pharma Pty Ltd; NSW Australia) or visually identical placebo tablets manufactured by a GMP compliant compounding pharmacy. These tablets will be administered up to four times commencing in the evening at the time of cervical ripening balloon catheter or prostaglandin insertion. The next day and at the time of the oxytocin intravenous infusion commencement, the second dose will be given, with a third dose 6 hours later and fourth and final dose 6 hours thereafter. If birth occurs before all four doses have been taken, no further tablets will be administered.

Outcomes:

Primary Outcome measure: Caesarean section

Secondary outcome measures:

1. Total Length of labour (including the duration of 1st, 2nd, 3rd stages of labour)
2. Induction commencement to birth interval
3. Total dose of oxytocin administered
4. Estimated blood loss in millilitres (from birth to 24 hours postpartum)
5. Instrumental vaginal birth (total and within 24 hours of IOL commencement)
6. Uterine tachysystole with fetal heart rate changes (CTG recordings)
7. Apgar score @ 5 minutes
8. Participant satisfaction with the labour

9. Postnatal length of stay
10. Admission of the baby to neonatal intensive care unit (from birth to discharge of the baby)
11. Participant melatonin levels will be determined prior to the administration of the second dose of the trial intervention and commencement of the oxytocin intravenous infusion, 3hrs after the administration of the second dose of the trial intention and within 20 minutes of giving birth.
12. Umbilical cord blood melatonin levels will be determined at the time of birth
13. Economic impact: The total resources and costs will be compared from the admission to the discharge of the participant and her baby. Economic outcome measures includes personnel costs, medication and other costs, this will be performed in compliance with the International Society for Pharmacoeconomics and Outcomes Research good practice standards

Covariates/Confounders

Maternal age (years), maternal weight and height at time of induction, maternal self-reported country of birth, Bishop score/cervical dilation at time of labour onset, pain relief in labour, time of birth and indication for operative birth, if relevant.

Sample and Data Collection:

Participant blood samples are collected: 1) prior to the second dose of tablets and before the commencement of the intravenous oxytocin infusion, 2) 3 hours after the oxytocin infusion has started 3) birth. Melatonin concentration will be measured using a commercial kit (RK-MEL2;

Buhlmann Laboratories, Schonenbuch, Switzerland). Prior to participant discharge from hospital all data relevant to the outcomes (including safety outcomes) will be collected by accessing hospital records. The participant will be visited in the postnatal ward by a member of the research team to ask for general feedback regarding their participation in the trial.

Confidentiality and data collection:

Confidentiality of all the participants data will be strictly maintained by all the researchers and in line with the national and local guidelines. All other members will be provided with the de-identified data (only with the unique participant code.) All data from the participants will be gathered on a standardized case report form and entered onto a password protected dedicated trial database which will be located in a secure, departmental location. Hard copy, case report form will be stored in a locked filling cabinet After the completion of the trial, the retention time of all trial related data and records will be for a minimum of 15 years in accordance with Monash Health and NHMRC requirements for clinical trials. After this retention period has been reached, all trial related records will undergo secure destruction.

Sample size

This trial has been powered to detect a 10% absolute reduction in the rate of the primary outcome: caesarean section. This was determined to reflect a clinically significant decrease in caesarean section rate as per the Healthypeople2020 targets, an initiative of the American Federal Government that recommends a 10% reduction in caesarean rates. The rate of caesarean section at term among women undergoing induction of labour at our health service is ~37%.

Therefore, to detect a reduction in caesarean section rates from 37 to 27% we will recruit a total of 722 women (361 in each arm). With a total of 722 women the detectable differences in each of our secondary outcomes are detailed below:

Secondary Outcomes	**Mean (SD) or Proportion in untreated group based on our data**	**2 sided detectable difference based on primary outcome sample size.**
Length of 1st stage of labour (hrs)	8.22(5.66)	-1.2 or 1.2 hours
Length of 2nd stage of labour (mins)	55(65)	-13.6 to 13.6 minutes
Length of 3rd stage of labour (mins)	6(13.6)	-2.8 to 2.8
Time on infusion (hrs)	7.22(4.46)	-0.93 or 0.93 hours
Total volume of oxytocin administered (milli units/min)	69.6(43)	-8.9 or 8.9 units
Blood loss(mls)	459.8(328)	-68.5 or 68.5mls
Apgar score <7 at 5 minutes	2%	0.0%, or 6.1%
Admission to NICU	1.3%	0.0% or 4.9%
Epidural Use	31%	22% or 41%

Statistical analysis:

All analyses will be performed using intention-to-treat and per-protocol if relevant. All data will be assessed for normality. Characteristics of the two groups will be tabulated and compared using the appropriate statistical test (chi^2, independent t-test, Mann-Whitney test). Differences in the primary outcome will be assessed by logistic regression adjusting for confounders/baseline imbalances between groups if appropriate. Differences in the secondary outcomes will be assessed using the appropriate regression method adjusting for confounders/baseline imbalances between groups if appropriate. The costs will be calculated separately for each mother/infant pair. The data will be assessed for normality and then compared between the melatonin and

control arm using the appropriate statistical test. A p value of <0.05 will be considered to indicate statistical significance. Analyses will be undertaken using StataCorp 12 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP.)

Adverse events

To date, clinical studies have not demonstrated any serious adverse reactions to the use of melatonin. However there may be unexpected adverse reactions associated with melatonin supplements when used at induction of labour in pregnant women. The participants and their babies will be assessed for any adverse events from the time of induction commencement to the completion of the trial. All adverse events regardless of the cause will be recorded and reported in accordance with the requirements of the sponsor, Monash health and NHMRC guidance. The responsibility for assessment, documentation and reporting all events is mainly by the Principal Investigator. Adverse event that occurs even after the discharge from the hospital will be reasonably related to the trial and will be reported to the sponsor by the PI.

Data and safety monitoring board:

As the use of melatonin is not indicated in current use in pregnancy for induction of labour, a Data and Safety Monitoring Board (DSMB) was established. The DSMB compromises of two Australian Health Professional Regulatory Agency (AHPRA) registered medical doctors, one a neonatologist and one obstetrician, as well as a biostatistician. Data will be provided to DSMB in a de-identified form following the recruitment of: 30%, and 60% participants, or at other times as requested by the DSMB or the Sponsor, Monash Health Research Directorate and Human Research Ethics Committee. No interim statistical analysis of the primary or secondary outcomes are planned. The DSMB are advised to advocate complete cessation, or re-evaluation, of the trial conduct, if it is evident that either arm of the trial is associated with a statistically significant

increase in or a 50% increased rate above the baseline ratio of any, or all, of the following outcome:

- Episodes of any or all of the following: uterine tachysystole (more than 5 contractions in 10 minutes without fetal heart rate changes), uterine hypotonus (defined as contractions lasting longer than 2 minutes in duration or occurring within 60 seconds of each other without fetal heart rate abnormalities) and uterine hyperstimulation(tachysystole or uterine hypotnous with fetal heart rate abnormalities)
- Estimated blood loss ≥ 500mls for vaginal birth or ≥ 750mls at caesarean birth.
- Participant entry to Intensive Care Unit (ICU), High Dependency Unit (HDU) or Coronary Care Unit (CCU)
- Uterine rupture
- Apgar score <7 at 5 minutes of age requiring active resusistation
- Maternal or perinatal death.

Trial modification and discontinuation:

There will be no allowance to the modification of the trial intervention. Participants may voluntarily elect to withdraw their participation in the trial at any time. The participant maybe or discontinued from the trial for reasons including not able to follow the procedures, in violation with the protocol, adverse drug reaction to the trial tablets or at their own request. The principal investigator will determine if any of the participants will need to be replaced.

The trial may be discontinued at the request of the Human Research Ethics Committee/Research Directorate or at the request of the Data Safety and Monitoring Committee (DSMB)

Patient and Public Involvement

There has been no patient or public involvement in the trial design. All women will be asked about their satisfaction with the induction of labour (secondary outcome measure) and feedback regarding their participation in the trial will also be sought.

Ethics and dissemination:

The clinical trial will be carried out in accordance with the conditions of Monash Health Human Research Ethics Committee (HREC approval), National Health Medical Research Council (NHMRC) *National Statement on Ethical Conduct in Human Research 2007* (updated 2018), and the NHMRC Australian Code for the Responsible Conduct of Research (2018)[29, 30]. On completion of the trial, its findings will be presented at scientific meetings and published in peer-reviewed journals.

Discussion:

The rates of induction of labour are increasing globally. The ultimate aim of induction of labour, beyond a healthy mother and baby, is to achieve a vaginal delivery. However, for up to 37% women having their labour induced this does not occur and they will require a caesarean section. This will be the first double-blind, randomised placebo controlled trial of melatonin administration at induction of labour. If successful it will show that an inexpensive supplement, given at induction will improve the rate of vaginal birth and reduce total healthcare costs. As such, this trial could be responsible for the first fundamentally new development in labour care for many decades

Trial Status:

Commenced March 2019

Funding

This trial is funded by a National Health and Medical Research Council (NHMRC) Project grant (APP1123498)

Authors' contributions

JCM, MDT and EW conceptualized the trial. JCM, MDT, EW, BM designed the trial and wrote the trial protocol. KS drafted the protocol manuscript for publication. All authors provided contributions to the editing and approval of the final manuscript.

Competing interests

KS: Nil

MDT: Nil

EW: None

BWM: None

JCM: None

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Abstract:

Introduction: Induction of labour is a common practice. In Australia up to 40% of women undergoing labour induction will ultimately have a caesarean section. As a biological role for melatonin in the onset and progress of labour has been demonstrated, we aim to test the hypothesis that addition of melatonin will reduce the need for caesarean section.

Methods and analysis: This is a double blind randomised, placebo-controlled trial in women undergoing induction of labour at term. We plan to randomise 722 women (1:1 ratio) to receive either melatonin (four doses of 10 mg melatonin: 1st dose – in the evening at the time of cervical balloon or Dinoprostone PGE_2 vaginal pessary insertion, 2nd dose –at time of oxytocin infusion commencement, 3rd dose- 6 hours after the second dose, 4th dose- 6 hours after the 3rd dose) or placebo (same dosing regime). The primary outcome measure will be the requirement for a caesarean section. Secondary outcomes will include duration of each stage of labour and time from induction to birth, total dose of oxytocin administration, epidural rate, indication for caesarean section, rate of instrumental deliveries, birth within 24 hours of induction commencement, estimated blood loss, Apgar score at 5 minutes, NICU admissions and participant satisfaction. Maternal melatonin levels will be measured immediately before administration of second dose of the trial intervention and 3 hours after the commencement of the oxytocin intravenous infusion and at the time of birth in order to determine any differences between the two trial arms.

Conclusion: This study will show if the addition of melatonin in women in whom labour is induced will improve labour outcomes.

Ethics and dissemination: The study is conducted in accordance with the conditions of Monash Health HREC (RES -17-0000-168A). Findings from the trial will be disseminated through peer-reviewed publications and conference presentations.

Trial registration number: ACTRN12616000311459, Universal trial number: (UTN) U1111-1195-3515. Trial Funding: NHMRC Project Grant APP1123498

KEYWORDS: Melatonin, Induction of Labour, Caesarean

Strengths and limitations of the study:

- This is the first randomised placebo controlled trial designed to study the effect of melatonin in reducing caesarean section rates
- Both the participants and the clinicians providing care will be blinded to the trial intervention allocation, thus decisions regarding the need for a caesarean section cannot be influenced by the allocation
- A potential limitation of this study is that it is conducted at a single health service.

Introduction:

Induction of labour (IOL) is one of the most common obstetric interventions. In Australia, the labours of 33% of women are induced, up from 25% only a decade earlier [1]. IOL is principally performed with the intent of reducing risks to the mother and/or baby by simply calling an end to the pregnancy. Ideally, the induced labour progresses to a vaginal birth However, despite randomised controlled trials indicating that IOL does not increase caesarean section rates [2, 3] outside of the tight confines of trials, the reality for women in high income nations is that up to ~40% of women having their labours induced will require a caesarean section, this is particularly true if they are nulliparous [4-8].

Failure of IOL resulting in a caesarean section is important for a number of reasons. Firstly, it may be associated with disappointment for the woman. There are well established links between the need for a caesarean birth and the risk of postnatal depression[9] and post-traumatic stress disorder , particularly in first time mothers[10]. Women who require a caesarean section are also less likely to breastfeed their baby [11, 12]. An intrapartum caesarean is associated with greater maternal morbidity than vaginal birth, including higher rates of postpartum haemorrhage, endometritis, venous thromboembolism, a longer recovery time and an increased rate of hospital readmission [13, 14]. Having a caesarean section is also associated with an increased risk of morbidities in subsequent pregnancies including preterm birth, abnormal placentation and uterine rupture [15, 16]. Improving the success of IOL is therefore important not only for the current labour, but all future pregnancies too.

It is most common practice in Australia, for the induction of labour process to begin in the morning. Optimum staffing levels are considered the main driver for this [17]. However, such timing may not be optimal for the woman. First formally reported over 60 years ago, was the observation that

spontaneous labour most commonly starts at night [18]. In a study of 19,000 labours the peak time of onset was between 2am and 3am [18]. More interestingly, labours commencing between 11pm and 1 am were significantly shorter than those that commenced between 4am and 7pm [18]. Over the years these intriguing observations have been confirmed by others (reviewed in [19]). The accepted explanation underlying the observations has been that uterine muscle (myometrial) fibres are more sensitive to the effects of endogenous oxytocin at night [20, 21]. The reason for this increased sensitivity at night is thought to be due to melatonin.

Melatonin (5-methoxy-N-acetyltryptamine) is an endogenous hormone produced primarily by the pineal gland. It provides circadian and seasonal timing cues [22]. In adults, melatonin levels remain low throughout the day. In the early evening the levels begin to increase peaking between 2am and 3am at night and then falling back down to low daylight concentrations again in the morning[23]. This circadian rhythm of melatonin is amplified in pregnancy. In particular, healthy pregnant women have higher concentrations of melatonin both at night and during the day compared to non-pregnant women [24] most likely due to *de novo* placental synthesis [25]. In addition, maternal melatonin levels increase with advancing gestation peaking during labour and then falling rapidly after birth [25]. The myometrium (uterine muscle) expresses the melatonin receptor MT2 and it is more highly expressed in labouring myometrium, collected at intrapartum caesarean section, than in myometrium from non-labouring women[26]. The role of melatonin in the onset of active labour has not been widely studied, however studies demonstrating increased myometrial expression of melatonin receptions amongst preterm birth suggests a role [26].Melatonin also increases the sensitivity of the myometrium to oxytocin-induced contractions [27]. Co-treatment of an immortalised myometrial cell line with melatonin and oxytocin resulted in a 2-fold increase in contractile response compared to oxytocin alone [27]. In these same studies melatonin was also

shown to increase the expression of the protein connexin 43, a gap-junction protein necessary for myometrial cell communication and the synchronization of uterine contractions[27]. Taken together, these *in vivo* and *in vitro* observations suggest that melatonin plays a biological role in the timing of onset of spontaneous labour, and in the effectiveness of spontaneous uterine contractions in labour. As IOL with an oxytocin intravenous infusion normally occurs during the daytime in the Australian setting, women do not experience the physiological increases in melatonin that occur prior to going into spontaneous labour at night, we hypothesise that administering melatonin at the time the induction process commences will reduce the IOL failure rate. We will undertake a double blind, randomized, placebo-controlled trial of oral melatonin administration at induction of labour to reduce caesarean section rates in healthy women with a singleton pregnancy at full term.

Methods and analysis:

This protocol has been designed in accordance with the SPIRIT 2013 Guidelines.

Study Design: Phase III double blind, randomised, placebo controlled trial.

Study setting: Participants will be recruited at Monash Health, Monash Medical Centre, a level six university affiliated teaching hospital in metropolitan Melbourne, that provides care for up to 9,000 women a year. Approximately 10 women who meet our inclusion/exclusion criteria are induced per week at this institution.

Subjects: Women with a singleton pregnancy who are undergoing induction of labour.

Inclusion criteria:

- ≥ 18 years and < 50 years of age
- Nulliparous or multiparous (para 1-3) women with a singleton pregnancy in cephalic presentation
- Full term (≥37 weeks)
- Women with previous caesarean section.
- Bishop's score < 5 (a strongest predictor of failure of induction) [28]
- Intact membranes
- Method of induction includes the use of a cervical balloon catheter or Dinoprostone PGE_2 (gel/tablets/pessary)
- No known significant maternal or obstetric medical condition that would affect melatonin pharmacokinetics or maternal safety

The specific exclusion criteria are:

- Fetal growth restriction (FGR) < 10th centile with Doppler changes
- Any known congenital anomaly of the fetus
- Any known abnormal karyotype of the fetus
- Non-reassuring fetal status
- Not willing to or inability to follow the procedures outlined in participant information and consent form
- Known allergy or sensitivity to melatonin and its formulation
- Mentally or legally incapacitated or not able to provide informed consent
- Participation in another trial where there is pharmaceutical or any other nutritional intervention

Participant recruitment and informed consent

Potential participants are those who are booked for labour induction from across the hospital's maternity departments. A researcher, not involved in the provision of clinical care, will approach all eligible women and provide the Participant Information and Consent Form. The researcher will then provide a verbal explanation of the trial, including a description of the trial processes, the voluntary nature of the trial and that a decision to participate, or not, will not affect their clinical care. The woman will be encouraged to discuss their participation with others of their choosing and given sufficient time to consider if they wish to take part, or not. If the woman agrees to participate, she will provide written informed consent.

Randomization and blinding

A perinatal epidemiologist with no involvement in the clinical trial will prepare the randomization sequence that is given to an onsite dedicated clinical trials pharmacy. Randomisation will occur

on a 1:1 ratio of melatonin to placebo. Both the melatonin and placebo tablets will be indistinguishable and contained in individual, pre -prepared bottles by the clinical trials pharmacist who is likewise not involved in participant recruitment of trial conduct. Neither the researcher, clinical staff nor the participants will know whether melatonin or placebo tablets have been administered. At the time of recruitment, each participant will be de-identified and assigned a unique trial code. Subsequently, all data and tissue samples collected from the participant will be labelled and stored only with this associated code.

Study intervention

Participants will be given either melatonin 10mg (Circadin® prolonged release melatonin, manufactured by Aspen Pharma Pty Ltd; NSW Australia) tablets or visually identical placebo tablets manufactured by a GMP compliant compounding pharmacy. These tablets will be administered up to four times commencing in the evening, the night before the ARM and commencement of the oxytocin infusion and at the time of cervical ripening balloon catheter or Dinoprostone PGE2 insertion. The next day and at the time of the oxytocin intravenous infusion commencement, the second dose will be given, with a third dose 6 hours later and fourth and final dose 6 hours thereafter. If birth occurs before all four doses have been taken, no further tablets will be administered.

Outcomes:

Primary Outcome measure: Caesarean section

Secondary outcome measures:

1. Total length of labour (including the duration of 1st, 2nd, 3rd stages of labour)
2. Induction commencement to birth interval (time of start of induction (either with balloon or cervidil or ARM and oxytocin) to the time of delivery.)

3. Total dose of oxytocin administered
4. Estimated blood loss in millilitres (from birth to 24 hours postpartum)
5. Instrumental vaginal birth (total and within 24 hours of IOL commencement)
6. Uterine tachysystole (more than five contractions in ten minutes without fetal heart rate changes)
7. Apgar score at 5 minutes
8. Participant satisfaction with the labour assessed via a five point likert scale (How would rate your overall experience of your induction?)
9. Postnatal length of stay
10. Admission of the baby to neonatal intensive care unit (from birth to discharge of the baby) as per the decision of Consultant Neonatologist.
11. Participant melatonin levels will be determined prior to the administration of the second dose of the trial intervention and commencement of the oxytocin intravenous infusion, 3hrs after the administration of the second dose of the trial intention and within 20 minutes of giving birth
12. Umbilical cord blood melatonin levels (collected at the time of birth)
13. Economic impact: The total resources and costs will be compared from the time of admission to the discharge of the participant and her baby. Economic outcome measures includes personnel costs, medication and other clinical costs, this will be performed in compliance with the International Society for Pharmacoeconomics and Outcomes Research good practice standards [29]

Covariates/Confounders

Maternal age (years), maternal weight and height at time of induction, parity, maternal self-reported country of birth, previous mode of birth for multiparous women, Bishop score/cervical dilation at time of labour onset, pain relief in labour, time of birth and indication for operative birth, if relevant.

Sample and Data Collection:

Participant blood samples are collected: 1) prior to the second dose of tablets and before the commencement of the intravenous oxytocin infusion, 2) 3 hours after the oxytocin infusion has started 3) birth. Melatonin concentration will be measured using a commercial kit (RK-MEL2; Buhlmann Laboratories, Schonenbuch, Switzerland). Prior to participant discharge from hospital all data relevant to the outcomes (including safety outcomes) will be collected by accessing their hospital records. The participant will be visited in the postnatal ward by a member of the research team to ask for general feedback regarding their participation in the trial.

Confidentiality and data collection:

Confidentiality of all the participants data will be strictly maintained by all the researchers and in line with the national and local guidelines. All members of the Data Safety Monitoring Board (DSMB) will be provided with de- identified data only (i.e. bearing only the unique participant code.) All data collected from the participants will be gathered on a standardized case report form and entered onto a password protected dedicated trial database. The original hard copy, case report form will be stored in a locked filling cabinet located in a secure, departmental location. After completion of the trial, all trial related data and records will be retained for a minimum of 15 years

in accordance with Monash Health and NHMRC requirements for clinical trials. After this period has been reached, all trial related data and records will be deleted or undergo secure destruction.

Sample size

This trial has been powered to detect a 10% absolute reduction in the rate of the primary outcome: caesarean section. This was determined to reflect a clinically significant decrease in caesarean section rate as per the Healthy people 2020 targets[30], an initiative of the American Federal Government that recommends a 10% reduction in caesarean rates. The rate of caesarean section at term among primiparous women undergoing induction of labour at our health service from 2009 to 2015 is ~37%. Therefore, to detect a reduction in caesarean section rates from 37 to 27% we will recruit a total of 722 women (361 in each arm). With a total of 722 women the detectable differences in each of our secondary outcomes are detailed below (Table 1).

Table 1. Detectable differences in secondary outcomes

Secondary Outcomes	**Mean (SD) or Proportion in untreated group based on our health service data**	**2 sided detectable difference based on primary outcome sample size.**
Length of 1st stage of labour (hrs)	8.22(5.66)	-1.2 or 1.2 hours
Length of 2nd stage of labour (mins)	55(65)	-13.6 to 13.6 minutes
Length of 3rd stage of labour (mins)	6(13.6)	-2.8 to 2.8
Duration of oxytocin infusion (hrs)	7.22(4.46)	-0.93 or 0.93 hours
Total volume of oxytocin administered (milli units/min)	69.6(43)	-8.9 or 8.9 units
Blood loss(mls)	459.8(328)	-68.5 or 68.5mls

Apgar score <7 at 5 minutes	2%	0.0%, or 6.1%
Admission to NICU	1.3%	0.0% or 4.9%
Epidural Use	31%	22% or 41%

Statistical analysis:

All analyses will be performed using intention-to-treat. All data will be assessed for normality. Characteristics of the two groups will be tabulated and compared using the appropriate statistical test (chi^2, independent t-test, Mann-Whitney test). Differences in the primary outcome will be assessed by logistic regression adjusting for confounders/baseline imbalances between groups if appropriate. Differences in the secondary outcomes will be assessed using the appropriate regression method adjusting for confounders/baseline imbalances between groups if appropriate. Rates of the primary and secondary outcomes will also be reported by parity. The costs will be calculated separately for each mother/infant pair. The data will be assessed for normality and then compared between the melatonin and control arm using the appropriate statistical test. A p value of <0.05 will be considered to indicate statistical significance. Analyses will be undertaken using StataCorp 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP.)

Adverse events

Adverse events and serious adverse events will be identified according to ICH GCP definitions. The Lead Principal Investigator who is an AHPRA registered medical doctor is responsible for all trial related medical decisions, this includes the assessment unexpected events and where necessary, attribution of causality to those which have been determined as adverse events.

To date, clinical studies have not demonstrated any serious adverse reactions to the use of melatonin. However, there may be unexpected reactions associated with melatonin when used at induction of labour in pregnant women that we do not yet know about. Therefore, participants and their babies will be assessed for any adverse events from the time of induction commencement until their discharge from hospital signifying their completion in the trial. All adverse events will be recorded and reported in accordance with the requirements of the Sponsor, Monash Health and NHMRC(National Health and Medical Research Council) guidance. The responsibility for the assessment, documentation and reporting of all such events is held by the Principal Investigator.

For the purposes of this clinical trial, it is reasonable to remain mindful of the potential for side effects and adverse reactions. The accompanying literature and/or product information for melatonin shows that adverse effects are **rare** i.e. likely to occur in fewer than 1 in 1,000 persons which includes:

Irritability, nervousness, restlessness insomnia, abnormal dreams, anxiety, migraine, lethargy, psychomotor hyperactivity (restlessness associated with increased activity), dizziness, somnolence (tiredness), high blood pressure, (upper) abdominal pain, indigestion, mouth ulceration, dry mouth, hyperbilirubinaemia (changes in the composition of your blood which could cause yellowing of the skin or eyes (jaundice), inflammation of the skin (dermatitis, night sweats, pruritis (itching), rash, dry skin, pain in extremities, menopausal symptoms, asthenia (feeling of weakness), chest pain, excretion of glucose in urine, excess proteins in the urine, abnormal liver function and weight increase, shingles, reduced number of white blood cells in the blood, decreased number of platelets in the blood, high level of fatty molecules in the blood, severe chest pain due to angina, feeling your heartbeat (palpitations). low serum calcium levels in the blood, low sodium levels in the blood,

altered mood, aggression, agitation, crying, stress symptoms, disorientation, early morning awakening, increased sex drive, depressed mood, depression, loss of consciousness or fainting, memory impairment, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, 'pins and needles' feeling (paresthesia) reduced visual acuity (visual impairment), blurred vision, watery eyes, dizziness when standing or sitting, vertigo, hot flushes, gastro-oesophageal reflux, gastrointestinal disorder, blistering in the mouth, tongue laceration, gastrointestinal upset, vomiting, abnormal bowel sounds, flatulence (wind), salivary hypersecretion (excess saliva production), halitosis (bad breath), abdominal discomfort, gastric disorder, inflammation of the stomach lining, eczema, erythema (skin rash), hand dermatitis, psoriasis, pruritic rash (itchy rash), nail disorder, arthritis, muscle spasms, neck pain, night cramps, tiredness, pain, thirst, passing large volumes or urine, presence of red blood cells in the urine, urination during the night, increased liver enzymes, abnormal blood electrolytes and abnormal laboratory tests.

Data and safety monitoring board:

As the use of melatonin is not indicated in current use in pregnancy for induction of labour, a Data and Safety Monitoring Board (DSMB) was established. The DSMB compromises of two Australian Health Professional Regulatory Agency (AHPRA) registered medical doctors, one a neonatologist and one obstetrician, as well as a biostatistician. Data will be provided to DSMB in a de-identified form following the recruitment of: 30%, and 60% participants, or at other times as requested by the DSMB or the Sponsor, Monash Health Research Directorate and Human Research Ethics Committee. No interim statistical analysis of the primary or secondary outcomes are planned. The DSMB are advised to advocate complete cessation, or re-evaluation, of the trial conduct, if it is evident that either arm of the trial is associated with a statistically significant increase in or a 50% increased rate above the baseline ratio of any, or all, of the following outcome:

- Episodes of any or all of the following: uterine tachysystole (more than 5 contractions in 10 minutes without fetal heart rate changes), uterine hypertonus (defined as contractions lasting longer than 2 minutes in duration or occurring within 60 seconds of each other without fetal heart rate abnormalities) and uterine hyperstimulation(tachysystole or uterine hypertonus with fetal heart rate abnormalities)
- Estimated blood loss ≥ 500mls for vaginal birth or ≥ 750mls at caesarean birth.
- Participant entry to Intensive Care Unit (ICU), High Dependency Unit (HDU) or Coronary Care Unit (CCU)
- Uterine rupture
- Apgar score <7 at 5 minutes of age requiring active resuscitation (this include oxygen therapy, intermittent positive pressure ventilation, endotracheal intubation, continuous positive airway pressure or laryngoscopy)
- Maternal or perinatal death.

Trial modification and discontinuation:

There will be no allowances to modify the trial intervention administration regimen or other trial related processes. The participant maybe or discontinued from the trial for reasons including not able to follow the procedures, in violation with the protocol, adverse drug reaction to the trial tablets or at their own request. The principal investigator will determine more participants will be needed to increase the sample size to compensate for loss to follow up/discontinuation/withdrawal. The trial may also be discontinued at the request of the Human Research Ethics Committee/Research Directorate or at the request of the Data Safety and Monitoring Committee (DSMB).

Patient and Public Involvement

There has been no patient or public involvement in the trial design. All women will be asked about their satisfaction with the induction of labour (secondary outcome measure) and feedback regarding their participation in the trial will also be sought.

Ethics and dissemination:

The clinical trial will be carried out in accordance with the conditions of Monash Health Human Research Ethics Committee (HREC approval), National Health Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research 2007 (updated 2018), and the NHMRC Australian Code for the Responsible Conduct of Research (2018)[31, 32]. On completion of the trial, its findings will be presented at scientific meetings and published in peer-reviewed journals.

Discussion:

The rates of induction of labour are increasing globally. The ultimate aim of induction of labour, beyond a healthy mother and baby, is to achieve a vaginal delivery. However, for up to 37% women having their labour induced this does not occur and they will require a caesarean section. The trial is the first double-blind, randomised placebo controlled trial of melatonin administration at induction of labour. If successful, it will show that this inexpensive sand safe supplement will improve the rate of vaginal birth and reduce total healthcare costs. As such, this trial could be responsible for the first fundamentally new development in labour care for many decades

Trial Status:

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Authors' contributions

JCM, MDT and EW conceptualized the trial. JCM, MDT, EW, BM designed the trial and wrote the trial protocol. KS drafted the protocol manuscript for publication. All authors provided contributions to the editing and approval of the final manuscript.

Competing interests

KS: None

MDT: None

EMW: None

BWM: None

JCM: None

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A Double-Blind Randomised Placebo Controlled Trial of Melatonin as an adjuvant agent in Induction of Labour (MILO): Study Protocol

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A Double-Blind Randomised Placebo Controlled Trial of Melatonin as an adjuvant agent in Induction of Labour (MILO): Study Protocol

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Abstract:

Introduction: Induction of labour is a common practice. In Australia up to 40% of women undergoing labour induction will ultimately have a caesarean section. As a biological role for melatonin in the onset and progress of labour has been demonstrated, we aim to test the hypothesis that addition of melatonin will reduce the need for caesarean section.

Methods and analysis: This is a double blind randomised, placebo-controlled trial in women undergoing induction of labour at term. We plan to randomise 722 women (1:1 ratio) to receive either melatonin (four doses of 10 mg melatonin: 1st dose – in the evening at the time of cervical balloon or Dinoprostone PGE_2 vaginal pessary insertion, 2nd dose –at time of oxytocin infusion commencement, 3rd dose- 6 hours after the second dose, 4th dose- 6 hours after the 3rd dose) or placebo (same dosing regime). Participants who are having artificial rupture of the membranes (ARM) only as the primary means of labour induction, will receive up to three doses of the trial intervention. The primary outcome measure will be the requirement for a caesarean section. Secondary outcomes will include duration of each stage of labour and time from induction to birth, total dose of oxytocin administration, epidural rate, indication for caesarean section, rate of instrumental deliveries, birth within 24 hours of induction commencement, estimated blood loss, Apgar score at 5 minutes, NICU admissions and participant satisfaction. Maternal melatonin levels will be measured immediately before commencement of the oxytocin intravenous infusion and 3 hours after and at the time of birth in order to determine any differences between the two trial arms.

Ethics and dissemination: The study is conducted in accordance with the conditions of Monash Health HREC (RES -17-0000-168A). Findings from the trial will be disseminated through peer-reviewed publications and conference presentations.

Protocol Version: V.7.0. 30th July 2019

Trial registration number: ACTRN12616000311459, Universal trial number: (UTN) U1111-1195-3515.

Trial Funding: NHMRC Project Grant APP1123498

KEYWORDS: Melatonin, Induction of Labour, Caesarean

Strengths and limitations of the study:

- This is the first randomised placebo controlled trial designed to study the effect of melatonin in reducing caesarean section rates
- Both the participants and the clinicians providing care will be blinded to the trial intervention allocation, thus decisions regarding the need for a caesarean section cannot be influenced by the allocation
- A potential limitation of this study is that it is conducted at a single health service.

Introduction:

Induction of labour (IOL) is one of the most common obstetric interventions. In Australia, the labours of 33% of women are induced, up from 25% only a decade earlier[1 2]. IOL is principally performed with the intent of reducing risks to the mother and/or baby by simply calling an end to the pregnancy. Ideally, the induced labour progresses to a vaginal birth However, despite randomised controlled trials indicating that IOL does not increase caesarean section rates [3 4] outside of the tight confines of trials, the reality for women in high income nations is that up to ~40% of women having their labours induced will require a caesarean section, this is particularly true if they are nulliparous [5-9].

Failure of IOL resulting in a caesarean section is important for a number of reasons. Firstly, it may be associated with disappointment for the woman. There are well established links between the need for a caesarean birth and the risk of postnatal depression[10] and post-traumatic stress disorder , particularly in first time mothers[11]. Women who require a caesarean section are also less likely to breastfeed their baby [12 13]. An intrapartum caesarean is associated with greater maternal morbidity than vaginal birth, including higher rates of postpartum haemorrhage, endometritis, venous thromboembolism, a longer recovery time and an increased rate of hospital readmission [14 15]. Having a caesarean section is also associated with an increased risk of morbidities in subsequent pregnancies including preterm birth, abnormal placentation and uterine rupture [16 17]. Improving the success of IOL is therefore important not only for the current labour, but all future pregnancies too.

It is most common practice in Australia, for the induction of labour process to begin in the morning. Optimum staffing levels are considered the main driver for this [18]. However, such timing may not be optimal for the woman. First formally reported over 60 years ago, was the observation that

spontaneous labour most commonly starts at night [19]. In a study of 19,000 labours the peak time of onset was between 2am and 3am [19]. More interestingly, labours commencing between 11pm and 1 am were significantly shorter than those that commenced between 4am and 7pm [19]. Over the years these intriguing observations have been confirmed by others (reviewed in [20]). The accepted explanation underlying the observations has been that uterine muscle (myometrial) fibres are more sensitive to the effects of endogenous oxytocin at night [21 22]. The reason for this increased sensitivity at night is thought to be due to melatonin.

Melatonin (5-methoxy-N-acetyltryptamine) is an endogenous hormone produced primarily by the pineal gland. It provides circadian and seasonal timing cues [23]. In adults, melatonin levels remain low throughout the day. In the early evening the levels begin to increase peaking between 2am and 3am at night and then falling back down to low daylight concentrations again in the morning[24]. This circadian rhythm of melatonin is amplified in pregnancy. In particular, healthy pregnant women have higher concentrations of melatonin both at night and during the day compared to non-pregnant women [25] most likely due to *de novo* placental synthesis [26]. In addition, maternal melatonin levels increase with advancing gestation peaking during labour and then falling rapidly after birth [26]. The myometrium (uterine muscle) expresses the melatonin receptor MT2 and it is more highly expressed in labouring myometrium, collected at intrapartum caesarean section, than in myometrium from non-labouring women[27]. The role of melatonin in the onset of active labour has not been widely studied, however studies demonstrating increased myometrial expression of melatonin receptions amongst preterm birth suggests a role[26]. Melatonin also increases the sensitivity of the myometrium to oxytocin-induced contractions[28]. Co-treatment of an immortalised myometrial cell line with melatonin and oxytocin resulted in a 2-fold increase in contractile response compared to oxytocin alone [28]. In these same studies melatonin was also

shown to increase the expression of the protein connexin 43, a gap-junction protein necessary for myometrial cell communication and the synchronization of uterine contractions[28]. Taken together, these *in vivo* and *in vitro* observations suggest that melatonin plays a biological role in the timing of onset of spontaneous labour, and in the effectiveness of spontaneous uterine contractions in labour. As IOL with an oxytocin intravenous infusion normally occurs during the daytime in the Australian setting, women do not experience the physiological increases in melatonin that occur prior to going into spontaneous labour at night, we hypothesise that administering melatonin at the time the induction process commences will reduce the IOL failure rate. We will undertake a double blind, randomized, placebo-controlled trial of oral melatonin administration at induction of labour to reduce caesarean section rates in healthy women with a singleton pregnancy at full term.

Methods and analysis:

This protocol has been designed in accordance with the SPIRIT 2013 Guidelines. (See Supplementary file 1. World Health Organization Trial Registration Data Set)

Study Design: Phase III double blind, randomised, placebo controlled trial.

Trial Timeline: March 2019–March 2022

Study setting: Participants will be recruited at Monash Health, Monash Medical Centre, a level six university affiliated teaching hospital in metropolitan Melbourne, that provides care for up to 9,000 women a year. Approximately 10 women who meet our inclusion/exclusion criteria are induced per week at this institution.

Subjects: Women with a singleton pregnancy who are undergoing induction of labour.

Inclusion criteria:

- ≥ 18 years and < 50 years of age
- Nulliparous or multiparous (para 1-3) women with a singleton pregnancy in cephalic presentation
- Full term (≥37 weeks)
- Bishop's score < 5 (a strongest predictor of failure of induction) [29]
- Intact membranes
- Method of induction includes the use of a cervical balloon catheter and/or Dinoprostone PGE_2 (gel/tablets/pessary) or women who are only having an amniotomy as the initial method of IOL

- No known significant maternal or obstetric medical condition that would affect melatonin pharmacokinetics or maternal safety

The specific exclusion criteria are:

- Fetal growth restriction (FGR) < 10th centile with Doppler changes
- Any known congenital anomaly of the fetus
- Any known abnormal karyotype of the fetus
- Non-reassuring fetal status
- Not willing to or inability to follow the procedures outlined in participant information and consent form
- Known allergy or sensitivity to melatonin and its formulation
- Mentally or legally incapacitated or not able to provide informed consent
- Participation in another trial where there is pharmaceutical or any other nutritional intervention

Participant recruitment and informed consent

Potential participants are those who are booked for labour induction from across the hospital's maternity departments. A researcher, not involved in the provision of clinical care, will approach all eligible women and provide the Participant Information and Consent Form (See Supplementary file 2). The researcher will then provide a verbal explanation of the trial, including a description of the trial processes, the voluntary nature of the trial and that a decision to participate, or not, will not affect their clinical care. The woman will be encouraged to discuss their participation with others of their choosing and given sufficient time to consider if they wish to take part, or not. If the woman agrees to participate, she will provide written informed consent.

Randomization and blinding

A perinatal epidemiologist with no involvement in the clinical trial will prepare the randomization sequence that is given to an onsite dedicated clinical trials pharmacy. Randomisation will occur on a 1:1 ratio of melatonin to placebo. Both the melatonin and placebo tablets will be indistinguishable and contained in individual, pre -prepared bottles by the clinical trials pharmacist who is likewise not involved in participant recruitment of trial conduct. Neither the researcher, clinical staff nor the participants will know whether melatonin or placebo tablets have been administered. At the time of recruitment, each participant will be de-identified and assigned a unique trial code. Subsequently, all data and tissue samples collected from the participant will be labelled and stored only with this associated code.

Study intervention

Participants will be given either melatonin 10mg (Circadin® prolonged release melatonin, manufactured by Aspen Pharma Pty Ltd; NSW Australia) tablets or visually identical placebo tablets manufactured by a GMP compliant compounding pharmacy. The administration regimen of the trial intervention will be determined by the method of labour induction:

Cervical balloon and/or Dinoprostone PGE_2 (pessary/tablet/gel) (evening admission)

Participants who are having a cervical balloon and/or Dinoprostone PGE_2 (pessary/tablet/gel), will receive up to four doses of the trial intervention: 1st dose – in the evening at the time of initial cervical balloon or Dinoprostone PGE_2 vaginal pessary/gel/tablet insertion, 2nd dose –at the time of the oxytocin intravenous infusion commencement, 3rd dose- 6 hours after the second dose, 4th dose- 6 hours after the 3rd dose.

Artificial rupture of membranes (ARM) only (morning admission)

Participants who are having artificial rupture of the membranes (ARM) only as the primary means of labour induction, will receive up to three doses of the trial intervention: 1st dose-following the ARM procedure-at the time of the oxytocin infusion commencement, 2nd dose- 6 hours after the first dose, 3rd dose- 6 hours after the 2nd dose.

For both of the trial intervention administration regimens, if birth occurs before all of the doses have been administered, no further tablets will be given.

Outcomes:

Primary Outcome measure: Caesarean section

Secondary outcome measures:

1. Total length of labour (including the duration of 1st, 2nd, 3rd stages of labour)
2. Induction commencement to birth interval (time of start of induction (either with balloon or cervidil or ARM and oxytocin) to the time of delivery.)
3. Total dose of oxytocin administered
4. Estimated blood loss in millilitres (from birth to 24 hours postpartum)
5. Instrumental vaginal birth (total and within 24 hours of IOL commencement)
6. Uterine tachysystole (more than five contractions in ten minutes without fetal heart rate changes)
7. Apgar score at 5 minutes
8. Participant satisfaction with the labour assessed via a five point Likert scale (How would rate your overall experience of your induction?)
9. Postnatal length of stay
10. Admission of the baby to neonatal intensive care unit (from birth to discharge of the baby) as per the decision of Consultant Neonatologist.

11. Participant melatonin levels will be determined prior to the administration of the second dose of the trial intervention and commencement of the oxytocin intravenous infusion, 3hrs after the administration of the second dose of the trial intention and within 20 minutes of giving birth
12. Umbilical cord blood melatonin levels (collected at the time of birth)
13. Economic impact: The total resources and costs will be compared from the time of admission to the discharge of the participant and her baby. Economic outcome measures includes personnel costs, medication and other clinical costs, this will be performed in compliance with the International Society for Pharmacoeconomics and Outcomes Research good practice standards [30]

Covariates/Confounders

Maternal age (years), maternal weight and height at time of induction, parity, maternal self-reported country of birth, Bishop score/cervical dilation at time of labour onset, pain relief in labour, time of birth and indication for operative birth, if relevant.

Sample and Data Collection:

Participant blood samples are collected: 1) just prior to commencement of the intravenous oxytocin infusion and intervention (tablet) administration, 2) 3 hours after the oxytocin infusion has started 3) birth. Melatonin concentration will be measured using a commercial kit (RK-MEL2; Buhlmann Laboratories, Schonenbuch, Switzerland). Prior to participant discharge from hospital all data relevant to the outcomes (including safety outcomes) will be collected by accessing their hospital

records. The participant will be visited in the postnatal ward by a member of the research team to ask for general feedback regarding their participation in the trial.

Confidentiality and data collection:

Confidentiality of all the participants data will be strictly maintained by all the researchers and in line with the national and local guidelines. All members of the Data Safety Monitoring Board (DSMB) will be provided with de- identified data only (i.e. bearing only the unique participant code.) All data collected from the participants will be gathered on a standardized case report form and entered onto a password protected dedicated trial database. The original hard copy, case report form will be stored in a locked filling cabinet located in a secure, departmental location. After completion of the trial, all trial related data and records will be retained for a minimum of 15 years in accordance with Monash Health and NHMRC requirements for clinical trials. After this period has been reached, all trial related data and records will be deleted or undergo secure destruction.

Sample size

This trial has been powered to detect a 10% absolute reduction in the rate of the primary outcome: caesarean section. This was determined to reflect a clinically significant decrease in caesarean section rate as per the Healthy people 2020 targets[31], an initiative of the American Federal Government that recommends a 10% reduction in caesarean rates. The rate of caesarean section at term among primiparous women undergoing induction of labour at our health service from 2009 to 2015 is ~37%. Therefore, to detect a reduction in caesarean section rates from 37 to 27% we

will recruit a total of 722 women (361 in each arm). With a total of 722 women the detectable differences in each of our secondary outcomes are detailed below (Table 1).

Table 1. Detectable differences in secondary outcomes

Secondary Outcomes	**Mean (SD) or Proportion in untreated group based on our health service data**	**2 sided detectable difference based on primary outcome sample size.**
Length of 1st stage of labour (hrs)	8.22(5.66)	-1.2 or 1.2 hours
Length of 2nd stage of labour (mins)	55(65)	-13.6 to 13.6 minutes
Length of 3rd stage of labour (mins)	6(13.6)	-2.8 to 2.8
Duration of oxytocin infusion (hrs)	7.22(4.46)	-0.93 or 0.93 hours
Total volume of oxytocin administered (milli units/min)	69.6(43)	-8.9 or 8.9 units
Blood loss(mls)	459.8(328)	-68.5 or 68.5mls
Apgar score <7 at 5 minutes	2%	0.0%, or 6.1%
Admission to NICU	1.3%	0.0% or 4.9%
Epidural Use	31%	22% or 41%

Statistical analysis:

All analyses will be performed using intention-to-treat. All continuous data will be assessed for normality. Characteristics of the two groups will be tabulated and compared using the appropriate statistical test (chi^2, independent t-test, Mann-Whitney test). Differences in the primary outcome will be assessed by logistic regression adjusting for confounders/baseline imbalances between groups if appropriate. Differences in the secondary outcomes will be assessed using the appropriate regression method adjusting for confounders/baseline imbalances between groups if appropriate. Rates of the primary and secondary outcomes will also be reported by parity. The

costs will be calculated separately for each mother/infant pair. A p value of <0.05 will be considered to indicate statistical significance. Analyses will be undertaken using StataCorp 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP.)

Adverse events

Adverse events and serious adverse events will be identified according to ICH GCP definitions. The Lead Principal Investigator who is an AHPRA registered medical doctor is responsible for all trial related medical decisions, this includes the assessment unexpected events and where necessary, attribution of causality to those which have been determined as adverse events.

To date, clinical studies have not demonstrated any serious adverse reactions to the use of melatonin. However, there may be unexpected reactions associated with melatonin when used at induction of labour in pregnant women that we do not yet know about. Therefore, participants and their babies will be assessed for any adverse events from the time of induction commencement until their discharge from hospital signifying their completion in the trial. All adverse events will be recorded and reported in accordance with the requirements of the Sponsor, Monash Health and NHMRC (National Health and Medical Research Council) guidance. The responsibility for the assessment, documentation and reporting of all such events is held by the Principal Investigator.

For the purposes of this clinical trial, it is reasonable to remain mindful of the potential for side effects and adverse reactions. The accompanying literature and/or product information for melatonin shows that adverse effects are **rare** i.e. likely to occur in fewer than 1 in 1,000 persons which includes:

Irritability, nervousness, restlessness insomnia, abnormal dreams, anxiety, migraine, lethargy, psychomotor hyperactivity (restlessness associated with increased activity), dizziness, somnolence (tiredness), high blood pressure, (upper) abdominal pain, indigestion, mouth ulceration, dry mouth, hyperbilirubinaemia (changes in the composition of your blood which could cause yellowing of the skin or eyes (jaundice), inflammation of the skin (dermatitis, night sweats, pruritis (itching), rash, dry skin, pain in extremities, menopausal symptoms, asthenia (feeling of weakness), chest pain, excretion of glucose in urine, excess proteins in the urine, abnormal liver function and weight increase, shingles, reduced number of white blood cells in the blood, decreased number of platelets in the blood, high level of fatty molecules in the blood, severe chest pain due to angina, feeling your heartbeat (palpitations). low serum calcium levels in the blood, low sodium levels in the blood, altered mood, aggression, agitation, crying, stress symptoms, disorientation, early morning awakening, increased sex drive, depressed mood, depression, loss of consciousness or fainting, memory impairment, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, 'pins and needles' feeling (paresthesia) reduced visual acuity (visual impairment), blurred vision, watery eyes, dizziness when standing or sitting, vertigo, hot flushes, gastro-oesophageal reflux, gastrointestinal disorder, blistering in the mouth, tongue laceration, gastrointestinal upset, vomiting, abnormal bowel sounds, flatulence (wind), salivary hypersecretion (excess saliva production), halitosis (bad breath), abdominal discomfort, gastric disorder, inflammation of the stomach lining, eczema, erythema (skin rash), hand dermatitis, psoriasis, pruritic rash (itchy rash), nail disorder, arthritis, muscle spasms, neck pain, night cramps, tiredness, pain, thirst, passing large volumes or urine, presence of red blood cells in the urine, urination during the night, increased liver enzymes, abnormal blood electrolytes and abnormal laboratory tests.

Data and safety monitoring board:

As the use of melatonin is not indicated in current use in pregnancy for induction of labour, a Data and Safety Monitoring Board (DSMB) was established. The DSMB compromises of two Australian Health Professional Regulatory Agency (AHPRA) registered medical doctors, one a neonatologist and one obstetrician, as well as a biostatistician. Data will be provided to DSMB in a de-identified form following the recruitment of: 30%, and 60% participants, or at other times as requested by the DSMB or the Sponsor, Monash Health Research Directorate and Human Research Ethics Committee. No interim statistical analysis of the primary or secondary outcomes are planned. The DSMB are advised to advocate complete cessation, or re-evaluation, of the trial conduct, if it is evident that either arm of the trial is associated with a statistically significant increase in or a 50% increased rate above the baseline ratio of any, or all, of the following outcome:

- Episodes of any or all of the following: uterine tachysystole (more than 5 contractions in 10 minutes without fetal heart rate changes), uterine hypertonus (defined as contractions lasting longer than 2 minutes in duration or occurring within 60 seconds of each other without fetal heart rate abnormalities) and uterine hyperstimulation(tachysystole or uterine hypertonus with fetal heart rate abnormalities)
- Estimated blood loss ≥ 500mls for vaginal birth or ≥ 750mls at caesarean birth.
- Participant entry to Intensive Care Unit (ICU), High Dependency Unit (HDU) or Coronary Care Unit (CCU)
- Uterine rupture
- Apgar score <7 at 5 minutes of age requiring active resuscitation (this include oxygen therapy, intermittent positive pressure ventilation, endotracheal intubation, continuous positive airway pressure or laryngoscopy)
- Maternal or perinatal death.

Trial modification and discontinuation:

There will be no allowances to modify the trial intervention administration regimen or other trial related processes. The participant maybe or discontinued from the trial for reasons including not able to follow the procedures, in violation with the protocol, adverse drug reaction to the trial tablets or at their own request. The principal investigator will determine more participants will be needed to increase the sample size to compensate for loss to follow up/discontinuation/withdrawal. The trial may also be discontinued at the request of the Human Research Ethics Committee/Research Directorate or at the request of the Data Safety and Monitoring Committee (DSMB).

Unblinding

Deliberate unblinding in the trial may occur in the following circumstances:

• To make clinical treatment decisions or when an unexpected serious adverse event occurs and the intervention must be made known.

• At the request of the Data Safety Monitoring Board

• At the conclusion of the study to determine the effect of the intervention.

For individual unblinding.

The lead clinical PI will assess and authorise the need for unblinding. The process for individual unblinding will involve the clinical PI contacting the site pharmacy and providing the participant identification number. Upon unblinding, the participant will be recorded as withdrawn from the trial.

Patient and Public Involvement

There has been no patient or public involvement in the trial design. All women will be asked about their satisfaction with the induction of labour (secondary outcome measure) and feedback regarding their participation in the trial will also be sought.

Ethics and dissemination:

The clinical trial will be carried out in accordance with the conditions of Monash Health Human Research Ethics Committee (HREC approval), National Health Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research 2007 (updated 2018), and the NHMRC Australian Code for the Responsible Conduct of Research (2018)[32 33]. On completion of the trial, its findings will be presented at scientific meetings and published in peer-reviewed journals.

Discussion:

The rates of induction of labour are increasing globally. The ultimate aim of induction of labour, beyond a healthy mother and baby, is to achieve a vaginal delivery. However, for up to 37% women having their labour induced this does not occur and they will require a caesarean section. The trial is the first double-blind, randomised placebo controlled trial of melatonin administration at induction of labour. If successful, it will show that this inexpensive sand safe supplement will improve the rate of vaginal birth and reduce total healthcare costs. As such, this trial could be responsible for the first fundamentally new development in labour care for many decades

Trial Status:

Commenced March 2019

Appendix 1. World Health Organization Trial Registration Data Set

Appendix 2. Patient Information and Consent Form.

Data Sharing: Consent from trial participants will also be sought to enable the sharing of de-identified data to assist with individual patient data meta-analyses with similarly planned trials.

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This trial is funded by a National Health and Medical Research Council (NHMRC) Project grant (APP1123498)

Authors' contributions

JCM, MDT and EW conceptualized the trial. JCM, MDT, EW, BM designed the trial and wrote the trial protocol. KS drafted the protocol manuscript for publication. All authors provided contributions to the editing and approval of the final manuscript.

Trial Sponsor:

Monash Health, 246 Clayton Road Victoria Australia 3168

Competing interests

KS: None

MDT: None

EMW: None

BWM: None

JCM: None

Protocol Amendments:

The PIs will be responsible for informing the Sponsor, Monash Health, of any proposed protocol amendments, in accordance with local requirements.

Dissemination policy:

Following completion of the trial, it is intended that the aggregated results will be published in peer reviewed journals and presented at scientific conferences. A summary of the trial findings will be provided to those participants who have requested to receive this.

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Standard Protocol Items: Recommendations for Interventional Trials trial data

Data category	Information
Primary registry and trial ID	Australian and New Zealand Clinical Trials Registry, ACTRN12616000311459
Date of registration in primary Registry	9/03/2016
Secondary identifying numbers	U1111-1195-3515
Source of funding or material Support	NHMRC Project Grant APP1123498
Primary sponsor	Monash Health
Secondary sponsor	Monash University
Contact for public queries	MDT miranda.davies@hudson.org.au
Contact for scientific queries	MDT miranda.davies@hudson.org.au
Public title	Melatonin supplementation during induction of labour to improve vaginal delivery rates (MILO)
Scientific title	A Double-Blind, Randomised, Placebo Controlled Trial of Melatonin as an adjuvant agent in Induction of Labour (MILO): Trial Protocol
Protocol version and date	V.7.0, 30th July 2019
Countries of recruitment	Australia
Health condition studied	Induction of labour
Interventions	Melatonin 10 mg (four doses) compared with placebo -For cervical balloon/Dinoprostone group Melatonin 10 mg (three doses) compared with placebo – For ARM group
Key inclusion and exclusion criteria	Inclusion criteria: Age >18 yrs and <50 yrs, Singleton, full term, nulliparous and multiparous (para 1-3) women with intact membranes with Bishop score <5, Method of Induction of labour (Balloon/ and/or Dinoprostone or ARM only), No significant maternal or obstetric medical condition that affect melatonin pharmacokinetics Exclusion criteria: Fetal growth restriction <10th centile with Doppler changes, known congenital abnormality of the fetus or abnormal karyotype, Non reassuring fetal status, Inability to follow the procedures outlined in the participant information/consent form, Known allergy/ sensitivity to melatonin, Mentally or legally incapacitated, Participation in another clinical

	trial where there is pharmaceutical or other nutritional intervention
Study type	Interventional Allocation: Randomisation Interventional Model: Parallel, placebo controlled Masking: Double-blind Phase III
Date of 1st enrolment	03/04/2019
Target sample size	722
Recruitment status	Recruiting
Primary outcome	Caesarean section
Key secondary outcomes	1)Total duration of labour, 2)Induction commencement to birth interval, 3)Estimated blood loss in mL, 4) Instrumental vaginal birth, 5) Uterine tachysystole, 6) Baby Apgar score at 5 min, 7) Participant satisfaction with the labour, 8) Economic impact

Participant Information Sheets and Consent Form

Monash Health and Jessie McPherson Private Hospital

Project Number	RES-17-0000-168A
Project Sponsor	Monash Health
Location	Monash Health and Jessie McPherson Private Hospital

Lead Principal Investigator

Professor Euan M. Wallace AM MBChB MD FRCOG FRANZCOG FAHMS
Carl Wood Professor of Obstetrics and Gynaecology, Monash University
Executive, The Ritchie Centre, Hudson Institute of Medical Research

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this clinical trial (research project) because your labour is being induced.

This Participant Information Sheet/Consent Form tells you about the clinical trial. It will explain what participation involves. Knowing what is involved will help you decide if you would like to take part in the research, or not.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with your partner, a relative, friend, or the doctor or midwife looking after you.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you choose to take part.

If you decide you want to take part in the clinical trial you will be asked to sign the Consent Form. By signing it you are telling us that you:

- understand what you have read
- consent to take part in the research project
- consent to have the tests and treatments that are described
- consent to the use of your personal and health information as described.

You will be given a copy of these Participant Information Sheets and signed Consent Form to keep.

2 What is the purpose of this research?

In Australia, about 1 in 3 women will undergo induction of labour (IOL). The ultimate goal for these women beyond a healthy baby, is to have a vaginal birth, thus avoiding the need for a caesarean section. However, some women undergoing IOL, particularly those who are having their first baby, will end up with a caesarean section. Indeed, of all women having their first baby who have their labour induced at Monash Health about 40% will ultimately require a caesarean section. Across Australia, this rate equates to about 22,000 caesarean sections each year.

When labour is induced, it usually involves the administration of an intravenous (into the vein) infusion ('drip'). The 'drip' contains a hormone called *oxytocin*. *Oxytocin* causes the uterus ('womb') muscle to contract leading to the cervix opening ('neck of the womb') and allowing the baby to descend and be born.

Laboratory studies have shown that the hormone *melatonin* also has effects on uterine muscle contractions and that *melatonin* and *oxytocin* work together to cause contractions. In some ways this is not surprising because we know that women will often go into labour by themselves during the night, when levels of *melatonin* within the body are at their highest. However, most hospitals – including Monash Health – start inductions of labour in the morning when melatonin levels at their lowest level. It is possible that increasing melatonin levels at the time of induction of labour might help with uterine contractions and so make the induction more likely to be successful.

The aim of our clinical trial is to find out if giving *melatonin* to women who are having their labour induced (IOL), will support and improve the effectiveness of their uterine contractions and so reduce the rate of caesarean section.

We would like to undertake the clinical trial in 722 mothers, who are having their labour induced (IOL) at full term (37 completed weeks, or more).

The use of *melatonin* to support uterine contractions during an induced labour has not been studied before. Therefore, its use in this clinical trial is regarded as 'experimental'. However, if successful, we hope that our findings may:

- Contribute to a reduction in the rate of caesarean section, following induction of labour (IOL).
- In the future, change, and improve, the care of women in labour (spontaneous onset or induced) everywhere.

3 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of *Monash Health*.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

4 What does participation in this clinical trial involve?

If you agree to participate in this clinical trial:

- We will ask you to read these Participant Information Sheets and sign the Consent Form.
- Using randomisation, we will allocate you into **one** of the two study groups: either to receive melatonin tablets **or** to receive tablets that do not contain any melatonin ('a placebo').

To make sure that all the information obtained from the research project is reliable and the best it can be, we have chosen to undertake the research project as a *randomised controlled trial (RCT)*. The RCT is regarded as the best way to test drugs, such as melatonin. The RCT method uses a process called 'randomisation' (like the flip of a coin) to allocate patients to the different study groups. Randomisation tries to make sure that the patients in each of the study groups are similar, and at the end of the research project, it allows us to interpret the results in a fair and appropriate way without jumping to conclusions.

The randomisation method of allocation means that you have an equal chance of being placed in either group. So as not to influence the results, neither you, the people caring for you or the researchers are able to choose the group that you are placed into.

- To take the study tablets containing either: melatonin 10mg or 'a placebo', a tablet(s) that does **not** contain any melatonin.

  The number of study tablets you will be given will depend upon your method of labour induction, for example, 'the cervical balloon' and/or the vaginal pessary (e.g. tablet/gel) or if you are only needing to have your 'waters' broken.

- For those women who are being induced using the cervical balloon or vaginal pessary, when you have been admitted to the hospital, around the time the cervical 'balloon' or a vaginal pessary is inserted you will be given a dose of the study tablets.

- Then, for all women, regardless of method of labour induction, a dose of study tablets will be given to you after your 'waters' have broken and once the oxytocin intravenous infusion ('drip') begins.

- The next dose of study tablets will be around 6 hours after the previous dose (if you have not had your baby).

- The next dose of study tablets, will be round 6 hours after the previous dose (if you have not had your baby).

There will be no more study tablets to take after this final dose.

NB. As soon as you have your baby, you will not need to take anymore of the study tablets. This means that some women will not be given all of the doses.

- We would like you to allow us to take **three,** separate, 10mL blood samples, so that we can measure your *melatonin* levels, as follows:

  - The first 10mL blood sample will be collected from you just before the oxytocin intravenous infusion ('drip') begins and the 2nd dose of the trial tablet(s) have been taken.
  - The second 10mL blood sample will be collected from you approximately 3 hours after the first blood sample.
  - The third, and last, 10mL blood sample will be collected from you, shortly after you have given birth.

Therefore, in total, **not more than 30mL of blood** will be required, this volume is equivalent to approximately six teaspoons and can safely be collected without risk of harm to you or your baby.

- After you have given birth and the placenta ('after birth') has completely separated from both you and your baby. We would like to collect a sample of blood (10mLs, or less) from the umbilical cord, in order to measure the melatonin levels in it. We do not need to touch your baby to be able to do this.

- After you have had your baby and you are either on the postnatal ward or at home, with your permission, we would like to ask you two questions regarding trial participation. This will take no more than 10 minutes of your time.

- To assist us to understand and present the results from our research project we will need to collect relevant information from your Monash Health (or Jessie McPherson Private Hospital) records with regard to: your health, pregnancy, birth and postnatal period. The final results will not have any information that could identify you, or any of the other participants, attached to it.

- Permit us to use the final results (only) of this research project in the planning of future, related research projects for which HREC (Human Research Ethics Committee) approval will be sought.

If you decide that you would like to participate in this research project, you will not be required to: stay in hospital any longer, return to the hospital after you have been discharged or complete any further paperwork other than signing the Consent Form.

5 Do I have to take part in this research project?

No, you don't. Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the research project at any stage.

Your decision whether to take part, or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Monash Health and Jessie McPherson Private Hospital.

If you decide to take part, you will be given this Participant Information and Consent Form to sign, and subsequently, a signed copy of these documents to keep.

6 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital.

Please note that whether you choose to participate in the research project, or not, your routine clinical care and the induction (IOL) processes do not change, this may include: the insertion of cervical 'balloon', having your waters 'broken', the use of an *oxytocin* intravenous infusion ('drip'), the collection of blood sample(s) and a requirement for an intravenous (IV) catheter ('bung').

7 What are the possible benefits of taking part?

There will be no clear benefit to you from your participation in this research project. However, we hope that the findings from the research project may change, and improve, the care of mothers in labour (spontaneous onset or induced) everywhere, in the future.

8 What are the possible risks and disadvantages of taking part?

- Melatonin

Melatonin has previously been tested in pregnant women in clinical trials and in women undergoing assisted reproduction, e.g. IVF (in vitro fertilization) procedures. These research studies would include those that have previously been conducted at Monash Health. Here, at Monash Health, we have used *melatonin* as a treatment for mothers who had problems in their pregnancies, such a pre-eclampsia (high blood pressure in pregnancy) and fetal growth restriction. These mothers received *melatonin* at similar doses to this induction of labour (IOL) trial. In those other studies women took melatonin for many days, or weeks. No side effects or adverse effects of melatonin on either a mother or her baby has been reported.

Animal studies to specifically investigate harmful effects of the use of melatonin during pregnancy have not shown any damage to the mother or fetus. These animal studies have used doses of *melatonin* that would be equivalent to a 100-times higher than the dose that we use in this study. As a result of this, *melatonin* has been assigned a TGA (Therapeutic Goods Administration) category B3 – a safe drug.

Melatonin has an excellent safety profile. As with any other medicine it can cause adverse reactions. These are considered to be **rare** i.e. likely to occur in fewer than 1 in 1,000 patients, and may include:

Irritability, nervousness, restlessness insomnia, abnormal dreams, anxiety, migraine, lethargy, psychomotor hyperactivity (restlessness associated with increased activity), dizziness, somnolence (tiredness), high blood pressure, (upper) abdominal pain, indigestion, mouth ulceration, dry mouth, hyperbilirubinaemia (changes in the composition of your blood which could cause yellowing of the skin or eyes (jaundice), inflammation of the skin (dermatitis, night sweats, pruritis (itching), rash, dry skin, pain in extremities, menopausal symptoms, asthenia (feeling of weakness), chest pain, excretion of glucose in urine, excess proteins in the urine, abnormal liver function and weight increase, shingles, reduced number of white blood cells in the blood, decreased number of platelets in the blood, high level of fatty molecules in the blood, severe chest pain due to angina, feeling your heartbeat (palpitations). low serum calcium levels in the blood, low sodium levels in the blood, altered mood, aggression, agitation, crying, stress symptoms, disorientation, early morning awakening, increased sex drive, depressed mood, depression, loss of consciousness or fainting, memory impairment, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, 'pins and needles' feeling (paresthesia) reduced visual acuity (visual impairment), blurred vision, watery eyes, dizziness when standing or sitting, vertigo, hot flushes, gastro-oesophageal reflux, gastrointestinal disorder, blistering in the mouth, tongue luceration, gastrointestinal upset, vomiting, abnormal bowel sounds, flatulence (wind), salivary hypersecretion (excess saliva production), halitosis (bad breath), abdominal discomfort, gastric disorder, inflammation of the stomach lining, eczema, erythema (skin rash), hand dermatitis, psoriasis, pruritic rash (itchy rash), nail disorder, arthritis, muscle spasms, neck pain, night cramps, tiredness, pain, thirst, passing large volumes or urine, presence of red blood cells in the urine, urination during the night, increased liver enzymes, abnormal blood electrolytes and abnormal laboratory tests.

As with any medication, there may be side effects caused by *melatonin* administration that the clinical staff caring for you do not expect or do not know about. Tell your doctor or midwife immediately about any new or unusual symptoms that you get.

If you are taking any medications, please tell the member of the research team, because some types of medication should not be combined with *melatonin* and as a result you would not be eligible to take part in this research study.

- Blood sampling

The total volume of blood (30mL) that you are being asked to donate to this research project, will not cause you harm. We will try to collect one of the blood samples at the same time as the intravenous cannula ('bung') is being sited for your routine clinical care.

Having a blood sample taken may cause you some discomfort or bruising. Sometimes, the blood vessel may swell, or blood may clot in the blood vessel, or the spot from which tissue is taken could become inflamed. Rarely, there could be a minor infection or bleeding. If this happens, it can be easily treated.

As with any research project, there may be additional risks that the researchers do not expect or do not know about.

If you do become upset or distressed as a result of your participation in this research project, the researcher is able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research team and will be provided free of charge. In addition, you may prefer to suspend or end your participation in the research project if distress occurs.

9 What will happen to my blood samples?

The blood samples you have provided to this research project will be used only for the purposes of this research project. The blood samples will be stored in The Ritchie Centre, Hudson Institute of Medical Research.

- All provided blood samples will be immediately de-identified at the time of collection and allocated a unique code. This means that any information which could identify you, such as: your name, address, date of birth and hospital record number will be removed before your blood sample(s) go into the laboratory for the scientists to look at.

We expect that all the blood samples we have collected from you will be needed for the melatonin analysis. However, after the *melatonin* analysis has been completed, if there is any blood left over, it will be thrown away.

10 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the researchers will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your Principal Investigator will make arrangements for your regular health/clinical care to continue. If you decide to continue in the research project you will be asked to sign an updated Consent Form.

Also, on receiving new information, the Principal Investigator might consider it to be in your best interests to withdraw you from the research project. If this happens, the Principal Investigator will explain the reasons and arrange for your regular health/clinical care to continue.

11 Can I have other treatments during this research project?

It is important to tell the researchers about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell the researchers about any changes to these during your participation in the research project.

MonashWomen's MonashHealth Maternity Services | MONASH University | The Ritchie Centre

12 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team. They will organise for you to sign the Withdrawal of Participation Form. Your withdrawal from this research project will in no way affect your routine clinical care, your relationship with those treating you, or your relationship with Monash Health or Jessie McPherson Private Hospital.

If you do withdraw your consent during the research project, the researchers will not collect any further blood samples or additional personal information from you. Although you should be aware that any blood samples or personal information that may have already collected will be retained and form part of the research project final results. This is necessary to ensure that the results of the research project can be measured properly and to

comply with the law. If you do not want the researchers to do this, you must tell them before you join the research project.

13 Could this research project be stopped unexpectedly?

It is unlikely this research project will be stopped unexpectedly but it would be stopped if:

- We discovered that participants in the research project were being compromised in any way.
- The sponsor of the research project, Monash Health, makes a request for the research project to stop.

14 What happens when the research project ends?

After you have had your baby and you are either on the postnatal ward or at home, with your permission, we would like to ask you two questions regarding trial participation. This will take no more than 10 minutes of your time. Once this has been completed, your participation in this research project ends. There will not be any further follow up. The research project itself will conclude once we have recruited 722 mothers and all data ('information') collection is complete.

If you would like a summary of the findings from this research project, please inform the named researcher:

Name	Ms Joanne C. Mockler
Position	Research Midwife Consultant, Manager (Obstetric) Perinatal Clinical Trials Department of Obstetrics and Gynaecology, Monash University and Monash Health
Telephone	+61 3 8572 2840
Email	joanne.mockler@monash.edu

15 Other relevant information about the research project

The funding for this research project is provided by: the Department of Obstetrics and Gynaecology, Monash University and a National Health Medical Research Council (NHMRC) New Investigator, Project Grant (App 1123498) awarded to Dr Miranda Davies-Tuck, Perinatal Epidemiologist, The Ritchie Centre, Hudson Institute of Medical Research

Additional costs
There are no additional costs associated with participating in this research project, nor will you be paid. All trial tablets i.e. *melatonin or* placebo*, that are* required to be taken as part of this research project will be provided to you free of charge.

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By signing the Consent Form, you consent to: the collection and use of your blood samples and any relevant information about you, that is required for the conduct of this Human Research Ethics Committee (HREC) approved research project.

Any information collected about you will only be disclosed to the researchers who are analysing your blood samples, with your permission, except as required by law. Any information will always be disclosed to them in a

de-identified form, that is without your, for example: name, initials, date of birth, address, telephone number or hospital record number being attached to it.

Any information obtained in connection with this research project that can identify you will remain confidential. This information will be stored in a locked filing cabinet and password-protected database, accessible only by the research team that have been approved by the Human Research Ethics Committee (HREC).

After the research project has been completed, the information will be securely stored for 15 years by the principal investigator, as currently recommended by the National Health and Medical Research Council (NHMRC) and Monash Health HREC. After this time, all the information will be disposed of in a secure and confidential manner.

In accordance with relevant Australian and Victorian privacy and other relevant laws, you have the right to request access to the information collected and stored by the research team about you. You also have the right to request that any information with which you disagree be corrected. Please contact the research team member named at the end of this document if you would like to access your information.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, Monash Health or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant named research personnel and regulatory authorities as noted above.

- Information about your participation in this research project will be recorded in your Monash Health or Jessie McPherson Private Hospital health records.

- It is anticipated that the results from this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

17 Injury

If you suffer any injuries or complications as a result of participating in this research project, you should contact the researchers as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian hospital.

18 Who is organising and funding the research?

The research project has been initiated by the named Lead Principal Investigator:- Professor Euan M. Wallace, Monash University. No member of the research team will receive a personal financial benefit from your involvement in the research project (other than their ordinary wages).

19 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you would like any further information concerning this research project, or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact:

Lead Principal investigator:

Name	Professor Euan M. Wallace
Position	Carl Wood Professor of Obstetrics, Monash University Executive, The Ritchie Centre, Hudson Institute of Medical Research.
Telephone	+61 3 9594 5145
Email	euan.wallace@monash.edu

Clinical contact person:

Name	Ms Joanne C. Mockler
Position	Research Midwife Consultant, Manager (Obstetric) Perinatal Clinical Trials Department of Obstetrics and Gynaecology, Monash University and Monash Health.
Telephone	+61 3 8572 2840
Email	joanne.mockler@monash.edu

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details:

Reviewing HREC name	Monash Health, Human Research Ethics Committee (HREC)
HREC Executive Officer	Mrs Deborah Dell Manager, Human Research Ethics Committee and Co-Manager, Research Support Services, Monash Health.
Telephone	+61 3 9594 4605
Email	*deborah.dell@monashhealth.org.au*

Local HREC office contact (Single Site -Research Governance Officer):

Name	Mr Michael Kios
Position	Research Governance Officer
Telephone	+61 3 9594 4606
Email	michael.kios@monashhealth.org

MonashWomen's MonashHealth Maternity Services

MONASH University

The Ritchie Centre

Consent Form

A Double-Blind, Randomised Placebo, Controlled Trial of Melatonin as an adjuvant agent in Induction of Labour

Project Number	RES-17-0000-168A
Project Sponsor	Monash Health
Location	Monash Health and Jessie McPherson Private Hospital
Lead Principal Investigator	Professor Euan M. Wallace

Declaration by Participant

- I have read the Participant Information Sheet or someone has read it to me in a language that I understand.
- I understand the purposes, procedures and risks of the research described in the project.
- I have had an opportunity to ask questions and I am satisfied with the answers I have received.
- I freely agree to participate in this research project as described and I understand that I am free to withdraw at any time during the research project without it affecting my future health care.
- I understand that I will be given a signed copy of this document to keep.

Name of participant (Please PRINT):

Signature: Date:

Witness* to participant's signature *(if applicable)* (Please PRINT):

Signature: Date:

* Witness is not to be the investigator, a member of the research team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by senior researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of the senior researcher (Please PRINT):

Signature: Date:

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation

A Double-Blind, Randomised Placebo, Controlled Trial of Melatonin as an adjuvant agent in Induction of Labour

Project Number	RES-17-0000-168A
Project Sponsor	Monash Health
Location	Monash Health and Jessie McPherson Private Hospital
Lead Principal Investigator	Professor Euan M. Wallace

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Monash Health or Jessie McPherson Private Hospital.

Name of Participant (please PRINT):

Signature: Date:

In the event that the participant's decision to withdraw is communicated verbally, the researcher will need to provide a description of the circumstances below.

Declaration by the senior researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of the senior researcher (Please PRINT):

Signature: Date:

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

SPIRIT CHECKLIST

Section/item	ItemNo	Description	Page No
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	Supplementary File
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	19
	5b	Name and contact information for the trial sponsor	19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6
	6b	Explanation for choice of comparators	6(placebo controlled)
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants,			

interventions, and outcomes Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	17
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended	10 -11
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions			

(for controlled trials) Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	18
Methods: Data collection, management, and analysis Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-13
	18b		17

		Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	21
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices	32		Appendix

Informed consent materials		Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A