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Effect of viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women: protocol for a pilot, feasibility randomised trial
Short Title: iPREM Pilot (Isolate to Prevent pretERM birth)

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Keywords:	COVID-19, SARS-CoV-2, NEONATOLOGY, OBSTETRICS

PROTOCOL PAPER

Long Title: Effect of viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women: protocol for a pilot, feasibility randomised trial

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Data Category	Information
Primary registry and trial identifying number	Australian New Zealand Clinical Trials Registry ACTRN12622000753752
Date registered	26 May, 2022
Source(s) of monetary or material support	Monash Health Monash University
Primary Sponsor	Monash Health
Secondary Sponsor	Monash University
Contact for Public and Scientific Queries	Associate Professor Atul Malhotra Email: atul.malhotra@monash.edu
Public Title	iPREM Pilot (Isolate to Prevent pretERM birth)
Scientific Title	Effect of viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women: protocol for a pilot, feasibility randomised trial
Countries of Recruitment	Australia
Health condition(s) studied	Premature birth
Intervention(s)	Active comparator: Pregnancy intervention mimicking COVID-19 viral mitigation measures
	Control comparator: Standard pregnancy care
Key inclusion and exclusion criteria	Inclusion: Pregnant women ≥18 years, previous preterm birth between 22-34 weeks gestation
	Exclusion criteria: Fetus with major congenital abnormality
Study Type	Interventional
	Allocation: randomized interventional model
	Primary purpose: feasibility
Date of first enrolment	July 2022
Target sample size	100
Recruitment status	Recruiting
Primary Outcome (s)	Feasibility
Secondary Outcome(s)	Preterm birth < 34 weeks, maternal quality of life and satisfaction and other pregnancy outcomes

Table 1: Trial Registration Data

ABSTRACT

Introduction: Preterm birth is a leading cause of perinatal morbidity and mortality. During the COVID-19 pandemic, reduction in rates of preterm birth in women exposed to viral mitigation measures was reported by multiple studies. In addition, others and we observed a more pronounced reduction of preterm birth in women who had previously experienced a preterm birth. The aim of this pilot study is to establish the feasibility of a lifestyle intervention based on viral mitigation measures in high-risk pregnancies, with the ultimate aim to reduce the incidence of preterm birth.

Methods and Analysis: One hundred pregnant women who have had a previous preterm birth between 22-34 weeks gestation will be recruited. This is a two-arm, parallel group, open-label randomised controlled feasibility trial: fifty women will be randomised to the intervention group, where they will be requested to comply with a set of lifestyle changes (similar to the viral mitigation measures observed during the pandemic). Another fifty women will be randomised to the control group, where they will undergo standard pregnancy care. The primary outcome of this trial is feasibility, which will be assessed by measuring patient eligibility rate, recruitment rate, compliance rate and data completion rate. Secondary outcomes include incidence of preterm birth, maternal satisfaction, maternal quality of life and other pregnancy outcomes. Standard methods in statistical analysis for randomised controlled trials on an intention to treat basis will be followed.

Ethics and Dissemination: This trial has been approved by the Monash Human Research Ethics Committee; approval reference number RES-22-0000-122A. Recruitment commenced in June 2022 and is expected to take around 12-18 months for completion. Study findings will be reported and submitted to peer-reviewed journals for publication, and presentation at conferences.

Trial Registration Number:

ACTRN12622000753752; pre-results.

ARTICLE SUMMARY

Strengths and Limitations of the Study

- This study is a randomised controlled trial.
- This is the first study of its kind to investigate the feasibility of a pregnancy intervention that mimics COVID-19 mitigation measures.
- Given the harsh nature of the lockdowns in Melbourne in 2020-21, we have a unique opportunity to investigate feasibility in a community that is well adapted to implementing restriction measures.
- Compliance to the intervention is self-reported.
- Due to the nature of the intervention, it is not possible to blind patients or clinicians involved in the recruitment process. However, the investigators collecting pregnancy outcomes and analysing data will be blinded to which group participants were allocated.

INTRODUCTION

Preterm birth, defined as delivery prior to 37 weeks gestation, is the leading cause of perinatal morbidity and mortality worldwide. Globally, approximately 15 million preterm births occur yearly and more than 1 million babies die shortly after birth as a direct result of their prematurity.(1) In Australia, 8.6% of deliveries are preterm with the average gestational age at birth being 33 weeks.(2) Preterm delivery occurs after the following obstetric precursors: spontaneous preterm labour (40-45%), preterm premature rupture of membranes (PPROM, 25-30%) or where delivery is indicated due to maternal or fetal compromise (30-35%).(3) An increasing degree of prematurity is known to correlate with a greater risk of complications including neurodevelopmental delay, cerebral palsy and cardio-respiratory disease.(4) Prematurity also has a significant economic impact; 72% of preterm infants will need admission to the neonatal intensive care unit where the average length of admission is 28 days and the cost per day is almost $2000.(2, 5) Mothers of preterm infants take longer to return to work, have a lower medium income and increased out of pocket healthcare costs. (6)

The exact causality of preterm birth remains unknown, however risk factors include previous preterm birth, maternal age, smoking, multiple gestation, gestational diabetes, maternal literacy level and social disadvantage.(3) Although we have methods to manage high risk women including progesterone treatments, aspirin and cervical cerclage, overall preterm birth rates have continued to rise in most industrialised nations. (7, 8)

The outbreak of COVID-19 brought the world to a standstill, having drastic social and economic impacts. The first Australian case was detected in Victoria in January 2020 and by March, measures including social distancing, wearing face masks and performing hand hygiene were introduced to mitigate virus spread.(9) Unexpectedly, it has been observed around the world that pregnant women exposed to mitigation measures for the COVID-19 virus have had a reduction in preterm birth rates by 20-30%, with this effect being more pronounced in early preterm birth (<34 weeks).(10-12) At Monash Health in Melbourne, an observational study demonstrated a 30% reduction in preterm birth rate prior to 34 weeks (risk ratio (RR) 0.74 (95% CI, 0.57-0.96; p = 0.021). This effect was stronger in women who had experienced a previous preterm birth (RR 0.42, 95% CI 0.21-0.82; p = 0.008) when compared to parous women who had not experienced a preterm birth (RR 0.93, 95% CI 0.63-1.28; p = 0.714).(13)

We hypothesise that in women with a previous preterm birth (<34 weeks), a pregnancy intervention mimicking COVID-19 mitigation measures will reduce the incidence of a subsequent preterm birth. We propose that the mechanism of action behind this effect may be due to a reduction in physical activity, stress, noise or air pollution, medical interventions and/or reduced rates of infection.

While observational studies, including those conducted by our team, have demonstrated that COVID-19 mitigation measures have an effect on preterm birth rates, these findings are inconsistent, it is unclear which aspect of these measures contribute to the phenomenon, and there have been no randomised controlled trials that have further investigated this effect to establish causality. We believe that we have a unique opportunity to study this effect further as we are based in Melbourne, where the population has been subject to some of the harshest lockdowns. However, we must first assess feasibility of such an intervention in pregnancy prior to conducting any larger randomised trials.

METHODS AND ANALYSIS

Study Design and Aim

This is a multi-site, two-arm open-label randomised controlled clinical trial. The Standard Protocol Items: Recommendations for Interventional Trials checklist was used to prepare this report.(14) The aim of this study is to investigate the feasibility of a lifestyle intervention in pregnancy that mimics viral mitigation measures in pregnant women who have previously had a preterm birth between 22-34 weeks.

Sample Size

Given the primary objective of this trial is to establish feasibility, we aim to recruit up to one hundred pregnant women, fifty of whom will be randomised to the intervention group and fifty of whom will be randomised to the control group.

Patient Population

Adult pregnant women receiving care at antenatal clinics who are at ‘high risk’ for having a preterm birth, where ‘high risk’ will be defined as having had a previous preterm birth between 22-34 weeks gestation.

Inclusion Criteria

Pregnant women, singleton or multiple gestation, will be eligible for this trial if they are aged 18 years or over and have previously delivered a preterm baby between 22+0 and 34+0 gestation, either spontaneously or iatrogenically.

Exclusion Criteria

Pregnant women will be excluded if they are carrying a fetus with one or more major congenital abnormalities.

Recruitment

Pregnant women who are enrolled in each recruitment site's antenatal clinics will be screened by a clinical team who are familiar with the eligibility criteria. We will make an entry onto the relevant medical records system flagging eligible women. We will also brief clinicians in the clinic on the study details so that they can refer any eligible patients we may have missed in our initial screening process. Additionally, we will display flyers advertising the study in clinic rooms so women who feel they are eligible can contact the research team themselves. When an eligible woman presents to the clinic, we will ask her treating clinician to briefly explain the study and provide her with a patient invitation form. A member of our research team will then approach eligible patients and explain trial details prior to recruitment. Prospective participants will be given 48 hours to consider whether they would like to take part in the trial. If the patient agrees to participate in the trial, they will be asked to sign a written consent form. We will ensure to obtain and store an individual record of all non-recruited patients, including their reasons for exclusion.

No members of the research team will be involved in the care of potential participants at the site of recruitment, ensuring that there are no unequal or dependent relationships. This study will not be blinded to participants as well as nurses, midwives, doctors, or investigators who are involved in the recruitment process. The investigator collecting study outcome data once a participant has completed the trial and the investigator who analyses the data will be blinded to the group to which participants were allocated.

Randomisation

Pregnant women who are successfully recruited are randomised and allocated on the first day of the trial using Research Electronic Data Capture (REDCap, Version 12.4.10, Vanderbilt University) by a member of the research team. REDCap is a secure, web-based data collection and management software that meets Health Insurance Portability and Accountability Act (HIPAA) compliance standards.(15, 16) The randomisation table was generated by using the statistical software Stata, with variable block sizes of 2 and 4.(17)

Interventions

Intervention Group

This pregnancy intervention is designed to mimic the stage 3 and 4 COVID-19 virus mitigation measures implemented in metropolitan Melbourne, Australia in 2020-21 (9). Alongside their standard pregnancy care, study participants will be asked to comply with the follow measures for the duration of the intervention. They should refrain from leaving their homes unless required to do so, such as shopping for essentials, to work or study, to seek or give care or for outside exercise. They should avoid having visitors to their home unless it is their intimate partner. Study participants should try to maintain social distancing where possible, that is, a 1.5m distance between themselves and another party unless in their own home or with an intimate partner. They will be asked to wear a face mask or covering when outside their home and perform hand hygiene prior to removing their mask or touching any aspect of their nose or mouth. Study participants should aim to remain at home between 9 pm and 5 am unless they are required to leave for work or study or to seek or give care and should avoid travelling beyond 5km of their place of residence except for essential reasons.

Control Group

Participants randomised to the control group will undergo standard pregnancy care without any restrictions.

Participants will begin the trial intervention two weeks prior to the gestational age at which the study participant's previous preterm birth occurred (i.e., if they delivered in their previous pregnancy at 32^{+3} weeks, their first day in the trial will be at 30^{+3} weeks). If the participant has had multiple preterm births, they will begin the trial 2 weeks prior to the gestational age of their earliest preterm delivery. The maximum gestation for recruitment will be 31 weeks to ensure that the participant is in the trial for at least 3 weeks. Therefore,

if they previously gave birth at 33^{+6} weeks gestation, they will be required to begin the study at 31 weeks gestation. The duration of the intervention will be six weeks (i.e., two weeks prior and four weeks post the gestational age of the previous preterm birth) or until 34 weeks gestation or until birth, whichever comes first.

Participants will be required to complete short, online surveys (which will be developed and distributed to their email via REDCap) to assess their self-reported compliance with the intervention, activities, mood and quality of life at baseline and then on a fortnightly basis for the duration of their time in the trial (see supplementary material).

Participants will also be encouraged to wear an actigraphy device (provided by the study team), similar to a watch, on their non-dominant wrist, 24 hours a day, for the duration of their time in the trial. For the purposes of this study, we have chosen the GENEActiv Original (Activinsights, Kimbolton, United Kingdom). It is a 43x40x13mm water resistant device, which has an inbuilt tri-axial piezoelectric accelerometer, light intensity and temperature sensors. The device will be set to record data at a sampling rate frequency of 20Hz. As sampling rate has a direct impact on the actigraph's battery life, this will enable the participant to wear the device for four weeks without requiring a re-charge. We will configure the device to automatically start recording on the participant's first day in the trial so they will not be required to push any buttons. If the participant remains in the trial for greater than four weeks, a research assistant will collect the old device from them and provide them with a new, charged device. Once the participant has finished their time in the trial, raw data will be downloaded from the devices using the GENEActiv PC Software (Version 3.3, Activinsights) as a '.bin' file and analysed.

Patient and Public Involvement

The study team consulted patients and clinicians at the antenatal clinic where recruitment is taking place for their advice and input into the design of the study.

OUTCOMES

Primary Outcome

Feasibility

We will measure feasibility using the following criteria:

Patient eligibility rate, which will be measured as the proportion of eligible women screened at the antenatal clinic who are expected to consent to taking part in this trial. We have set a pre-defined target of 50%.

Patient recruitment rate, which will be measured as the proportion of eligible women that consent to taking part in the study who are randomised (noting that there may be a significant time period between consent and randomisation). We have set a pre-defined target of 50%.

Compliance rate, which will be measured as the proportion of participants in the intervention group who are considered to have good compliance with the intervention. This will be measured via fortnightly, participant filled surveys and we will set a pre-defined target of 75%. On each fortnightly survey, participants will be asked questions pertaining to their compliance with each restriction measure. For example, participants will be asked how often they wore a mask when outside their home and if they were to answer either 'most of the time' or 'all of the time', we would classify this as having $\geq$ 75% compliance with this restriction measure. Participants must report $\geq$ 75% compliance for all restriction measures in order to be defined has having 'good compliance' with the intervention. This will be measured at the end of the trial.

Data completion rate, which will be measured as the proportion of trial participants who complete the final survey (i.e., the survey that the participant is required to complete once they reach an endpoint). This will be measured at the end of the trial. We have set a pre-defined target of $\geq$ 75%.

Secondary Outcomes

Secondary outcomes will include incidence of preterm birth prior to 34 weeks gestation, maternal satisfaction, and quality of life as well as other pregnancy outcomes such as pregnancy duration, incidence of stillbirth and incidence of iatrogenic or spontaneous delivery. We will measure maternal satisfaction and quality of life via fortnightly surveys we have developed based on previously validated questionnaires including but not limited to the Beck Depression Inventory, QOL-GRAV and Multidimensional Scale of Perceived Social Support. We will also collect non-dominant wrist raw acceleration data through the

actigraphy device. The raw acceleration data will be used to derive physical activity patterns, estimate sleep-wake cycle and verify the compliance with wearing the device.

Other Data to be Collected

Demographic data collected will include maternal demographic data such as birth country, age, marital status, medical history, drug use, risk factors for preterm birth, gravida/parity, obstetric history, details of current pregnancy, incidence of prelabour premature rupture of membranes, incidence of presumed chorioamnionitis, use of antenatal steroids, mode of delivery and maternal death. We will also collect infant demographic data such as birthweight in grams.

Other neonatal outcomes collected will include incidence of admission to neonatal intensive care (NICU) or special care nursery (SCN), incidence of NICU stay >48 hours, neonatal morbidity (5-minute Apgar score <5, respiratory distress syndrome requiring intubation, grade 3 or 4 intraventricular haemorrhage, neonatal seizures, culture-positive neonatal sepsis, retinopathy of prematurity requiring treatment, necrotising enterocolitis) and neonatal death.

DATA ANALYSIS

We will use the open-source package GENEActiv and GENEA In R (GGIR, Version 2.5) to translate raw actigraphy data to readable information.(18) Data will be downloaded from each device as a .bin file, which will be read and translated to a .csv file by the GGIR package according to predefined parameters. Initially, GGIR will perform sensor calibration in the data collected to check and correct calibration errors in the accelerometer(19). Due to the raw data size, we will set GGIR to summarise the collected 20hz sample-rate data to 5s epochs.

Feasibility targets will be assessed first. Baseline continuous covariates will be expressed as mean and standard deviation or median and interquartile range depending on the distribution of the data as assessed by inspection of histograms and quantile-quantile (QQ) plots. Normally distributed continuous variables will be compared between the groups using independent-samples t-test, and non-normally distributed variables will be compared between the trial arms with the Wilcoxon rank-sum test.

Categorical variables will be expressed as counts and percentages and compared between the study groups using the Chi-squared test or Fisher's exact test, as appropriate. Descriptive statistics will be reported for assessment of feasibility as previously defined in the study outcomes section.

The effect of the intervention on the odds of preterm birth and other binary pregnancy outcomes will be modelled using univariable logistic regression models and expressed as the odds ratio with 95% confidence intervals. Multivariable models will be used to adjust for covariates with significant imbalances between the groups at baseline, if needed. Analyses will be performed according to an intention-to-treat principle, and secondary per protocol analysis will be performed including only participants from the intervention group with compliance ≥ 75%.

All statistical analyses will be conducted in the statistical environment R, and p-values below 0.05 will be considered statistically significant. We will report findings in accordance with Consolidated Standards of Reporting Trials guidelines.

ADVERSE EVENTS

Serious Adverse Events (SAE)

SAEs will be defined as any event required admission to hospital (excluding admission for delivery), maternal or fetal death, fetal malformations, any event that leads to maternal disability and any event where a participant contacts the study team with concerns regarding a serious deterioration in their mental health during the trial.

Adverse Events (AE)

Any other event reported by a participant or their partner not needing hospital admission or not falling in a category of SAEs.

DATA SAFETY MONITORING BOARD (DSMB)

An independent DSMB comprising of a senior research fellow in obstetrics and gynaecology, a consultant neonatologist and a perinatal epidemiologist has been formed to review the study, the data generated and ensure safety of all participants. Members of the DSMB do not have a vested financial, scientific, or other conflict of interest with this trial. All SAEs will be reported to the data safety monitoring board (DSMB) within 24-48 hours of the team becoming aware of the event.

An interim analysis evaluating the safety of the trial will be conducted after fifty eligible women have been screened. The DSMB will be required to evaluate any adverse events and assess the ongoing safety of the trial. They will have the ability to suspend or terminate the study if required on the basis of a lack of feasibility or any SAEs observed. Given the feasibility nature of the trial and that the interim analysis will only assess safety, no sequential trial adjustments to the alpha level will be made.

REPORTS TO HUMAN RESEARCH ETHICS COMMITTEE (HREC)

Any SAEs that the DSMB deem will necessitate a temporary halt of the trial pending review and any changes to the protocol or patient information consent form (PICF) will be reported to the HREC. We will also ensure to provide an interim report following the recruitment of fifty participants to the trial as well as an annual research progress report.

ETHICS AND DISSEMINATION

Ethics

This study has been approved by the Monash Health Human Research Ethics Committee and will be conducted in accordance with the approved protocol/amendment(s) and NHMRC National Statement on Ethical Conduct in Human Research 2007 (updated 2018). The study will also comply with the Declaration of Helsinki and with the Good Clinical Practice (GCP) standards. An expert team of senior obstetricians, neonatologists, researchers and psychiatrists were consulted regarding the intervention and protecting the psychological safety of the women in the trial. We have ensured that participants have ample opportunity to contact the study team if they are concerned and have developed the surveys in consultation with a psychiatrist to appropriately assess the quality of life of trial participants.

Data for this trial will be collected from electronical medical records system, surveys completed by participants and from actigraphs utilised by participants following informed consent. Each participant will be assigned a unique participant identifier which will be the only number that appears on their reports to maintain confidentiality. Only authorised members of the research team will be able to log into the secure web-based portal, REDCap, to input trial data for each participant using their unique participant identifier. Deidentified actigraph device data will be stored in a password protected computer file,

also only accessible to authorized members of the research team. All data will be stored for 15 years after which it will be disposed of via permanent deletion.

Consent

Informed, written consent will be obtained using a specifically designed PICF (see supplementary material) from potential participants after a member of the research team has ensured that the participant understands the study procedures involved, the potential benefits and/or risks as well as the expected duration of the intervention. Participants will be made aware that their participation is entirely voluntary and that they are free to withdraw at any stage for any reason. The research team member will also inform participants that withdrawal of consent will not affect their relationship with their physician or their right to appropriate medical treatment.

Dissemination

The study results will be disseminated by publication in peer-reviewed journals and presented at conferences as appropriate.

OTHER

Author Contributions: The initial concept was developed by AM, DLR and BWM. All authors contributed to the design of the study. Shivadharshini S drafted the ethics application, protocol, case report forms, surveys and manuscript. AM, DLR, BWM, RCP, RTS, FB-J, DM and JS made critical revisions and assisted with ethics application submission, editing of protocol and editing of manuscript. All authors have read and approved the final manuscript and are accountable for its accuracy.

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Competing Interests: None declared

Patient Consent for Publication: Not required

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REFERENCES

1. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller A-B, et al. Born Too Soon: The global epidemiology of 15 million preterm births. Reproductive Health. 2013;10(1):S2.
2. Welfare AIoHa. Australia's Mothers and Babies 2016 - in brief. Perinatal Statistics Series. Canberra: Australian Institute of Health and Welfare; 2018.
3. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. The Lancet. 2008;371(9606):75-84.
4. Organization WH. Born Too Soon. The Global Action Report on Preterm Birth. Geneva: World Health Organization; 2012.
5. Zainal H, Dahlui M, Soelar SA, Su TT. Cost of preterm birth during initial hospitalization: A care provider's perspective. PloS one. 2019;14(6):e0211997-e.
6. Fox H, Callander E. Cost of preterm birth to Australian mothers: Assessing the financial impact of a birth outcome with an increasing prevalence. Journal of Paediatrics and Child Health. 2021;57(5):618-25.
7. Chawanpaiboon S, Vogel JP, Moller A-B, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. The Lancet Global Health. 2019;7(1):e37-e46.
8. Newnham JP, Dickinson JE, Hart RJ, Pennell CE, Arrese CA, Keelan JA. Strategies to prevent preterm birth. Frontiers in immunology. 2014;5:584-.
9. Storen RC, N. COVID-19: a chronology of state and territory government announcements (up until 30 June 2020). In: Services P, editor. Canberra: Parliamentary Library 2020.
10. Philip RK, Purtill H, Reidy E, Daly M, Imcha M, McGrath D, et al. Unprecedented reduction in births of very low birthweight (VLBW) and extremely low birthweight (ELBW) infants during the COVID-19 lockdown in Ireland: a 'natural experiment' allowing analysis of data from the prior two decades. BMJ Global Health. 2020;5(9):e003075.
11. Been JV, Burgos Ochoa L, Bertens LCM, Schoenmakers S, Steegers EAP, Reiss IKM. Impact of COVID-19 mitigation measures on the incidence of preterm birth: a national quasi-experimental study. The Lancet Public Health. 2020;5(11):e604-e11.
12. Matheson A, McGannon CJ, Malhotra A, Palmer KR, Stewart AE, Wallace EM, et al. Prematurity Rates During the Coronavirus Disease 2019 (COVID-19) Pandemic Lockdown in Melbourne, Australia. Obstetrics & Gynecology. 2021;137(3).
13. Rolnik DL, Matheson A, Liu Y, Chu S, McGannon C, Mulcahy B, et al. Impact of COVID-19 pandemic restrictions on pregnancy duration and outcome in Melbourne, Australia. Ultrasound in Obstetrics & Gynecology. 2021;58(5):677-87.
14. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Annals of internal medicine. 2013;158(3):200-7.
15. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.
16. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
17. StataCorp. Stata Statistical Software: Release 17. 17 ed. College Station, TX: StataCorp LLC; 2021.
18. Migueles JH, Rowlands AV, Huber F, Sabia S, van Hees VT. GGIR: A Research Community–Driven Open Source R Package for Generating Physical Activity and Sleep

Outcomes From Multi-Day Raw Accelerometer Data. Journal for the Measurement of Physical Behaviour. 2019;2(3):188-96.
19. Hees VTv, Fang Z, Langford J, Assah F, Mohammad A, Silva ICMd, et al. Autocalibration of accelerometer data for free-living physical activity assessment using local gravity and temperature: an evaluation on four continents. Journal of Applied Physiology. 2014;117(7):738-44.

Effect of viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women: protocol for a pilot, feasibility randomised trial

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SUPPLEMENTARY MATERIAL

PARTICIPANT INFORMATION AND CONSENT FORM (MASTER)

Title	Randomised controlled trial investigating the effect of viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women
Short Title	iPREM (Pilot)
Project Sponsor	Monash Health
Principal Investigator(s)	Professor Ben Mol
Associate Investigator(s)	Dr A/Prof Daniel Rolnik A/Prof Atul Malhotra Dr Shivadharshini Sridhar

Part 1 What does the participation involve?

1 Introduction

We are inviting you to take part in this research project because you are currently pregnant and have previously given birth to a preterm baby (i.e. a baby born between 22 and 34 weeks of gestation). Your information was obtained from our medical records system.This research project is investigating the feasibility and safety of an intervention in pregnancy that may decrease the risk of preterm birth.

This participant information and consent form will explain the purpose of our project and what it will involve as clearly as possible so that you can be fully informed before you decide whether you would like to take part.

Please take your time to read through this statement carefully. If you have any questions or concerns, please do not hesitate to contact our researcher via email or phone. Before deciding whether you would like to participate, you may want to talk about it with a family member or a medical professional.

Participation in this research project is voluntary and if you decide you do not wish to take part, you do not have to. You will still receive the best possible care regardless of whether you are involved with our study.

If you do decide to take part, you will need to sign the consent section. By signing this, you are telling us that:

- You understand everything you have read in this statement
- You consent to your participation in this project
- You consent to the use of your personal and health information as described

You will be given a copy of this participant information and consent form to keep.

2 What is the purpose of this research?

Preterm birth (i.e. when a baby is born too early) occurs in around 9% of all deliveries in Australia and can be associated with significant medical consequences for babies. During the COVID-19 pandemic, we, and many other groups around the world have observed that women who have been pregnant during lockdown have experienced a decreased rate of preterm birth. At Monash Health, a 30% decrease in women giving birth before 34 weeks of gestation was observed and this effect was stronger in women who had a previous preterm birth. We believe that this phenomenon may have to do with changes in the way we lived during lockdowns - physical distancing, changes in physical activity, work from home and possibly improved hygiene.

The purpose of this study is to investigate whether it is feasible to conduct an intervention in pregnancy that mimics the COVID-19 lockdowns and observe if there is an associated decrease in the rate of preterm birth in women who have previously experienced a preterm birth. Once we can establish feasibility and safety of this intervention, larger studies may be conducted to further establish whether these measures actually decrease preterm birth rates.

This research has been initiated by a research team led by Professor Ben Mol. This team, alongside the associate investigators listed above have experience looking after pregnant women and premature babies.

3 Who is organising and funding the research?

This research project is being conducted and led by Professor Ben Mol and his research team.

4 What does participation in this research involve?

If we determine that you are eligible to participate and you choose to take part in this study, you will be required to sign the consent form below.

We are inviting 100 women to take part in this study. 50 women will be randomly assigned to the 'control' group and undergo standard pregnancy care with no changes. 50 women will be randomised to the 'intervention' group, where they will be asked to comply with a pregnancy intervention that mimics the lockdown measures implemented in Melbourne to prevent the transmission of COVID-19.

If you are part of the pregnancy intervention group, you will be asked to try and comply with the following measures to the best of your ability for the duration of the study:

- Refrain from attending social gatherings and maintain 1.5m distance between yourself and another individual when outside your home
- Try to wear a face mask or covering whenever you leave your home
- Try to perform hand hygiene prior to touching your nose or mouth
- Try to remain in your home unless you must leave for study/work, for essential services, to seek, safety purposes (e.g you do not feel safe in your home) or give care or to do outdoor exercise
- Try to remain at home between the hours of 9pm-5am unless you must leave for work/study, safety purposes or to seek/give care
- Avoid having visitors to your home unless they are an intimate partner
- Try not to travel beyond 5km from your place of residence

We understand that there may be certain circumstances that mean you cannot follow through with all the above recommendations, for example, important events that you must attend such as a wedding or funeral. You are of course free to attend at your discretion, we just ask that wherever you can, please try to follow the recommendations as much as possible. For instance, if you attend a wedding, consider following at least some of the recommendations such as wearing a facemask and performing hand hygiene.

The study will begin 2 weeks before the gestation at which you gave birth to your previous preterm baby (i.e. if you gave birth at 32 weeks, the study would begin at 30 weeks gestation of your current pregnancy). However, if your previous preterm baby was born at 33+6 weeks gestation, the study will begin at 30+6 weeks gestation of this pregnancy so that you are in the study for at least 3 weeks. It will be conducted for 6 weeks (i.e. 2 weeks before and 4 weeks after the gestational age of your previous preterm birth), until 34 weeks gestation or until birth – whichever comes first.

You will be asked to complete a 5-10 minute fortnightly surveys over the course of the study about your work, household contacts, physical activity, hygiene practices, mood and quality of life. You will also be asked to wear a device on your wrist (figure 1), similar to a watch, that will record physical activity, temperature, light and sleep for the duration of your time in the study.

Figure 1. Actigraphy device.

You will not be paid to take part in this research project and there will be no additional costs to you associated with your participation.

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

Participation in this trial is entirely voluntary and if you do not wish to take part you are in no way obligated to. If you decide to take part and then change your mind, you are free to withdraw at any stage – you can easily do this by contacting the researcher via email or phone and informing them of your wish to withdraw.

If you do decide to take part, you will be given a copy of this patient information consent form to sign and a copy to keep.

Your decision to take part, or not take part in this study will not affect your relationship with your doctors, midwives, or the health service, and will not impact the care that you are given.

6 What are the alternatives to participation?

You do not have to take part in this study to receive treatment at this hospital. Your routine pregnancy care will not change or be impacted if you decide not to take part.

7 What are the possible benefits of taking part?

This research may provide us with further insight into prevention of preterm birth and could play an integral role in changing future clinical practice. We are conducting this study to mainly check whether such a pregnancy intervention is feasible and safe, and we are not yet sure if/which

aspect of lockdown measures impact preterm birth rates. As such, there may be no clear benefit for your pregnancy from your participation.

Given the COVID-19 pandemic is still ongoing, a potential benefit for anyone who is in the intervention group of the study is that they may be less likely to contract the virus given they will be adhering to established viral mitigation measures, that is, restrictions to travel/social distancing/physical contact and recommendations regarding hygiene/face coverings known to prevent transmission.

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

We anticipate that the main risks associated with participating in this study are feelings of social isolation and perhaps decreased social support in those who are a part of the pregnancy intervention group. You may also find that the additional restrictive measures imposed may make it more difficult to perform your routine tasks, for example, you may have to shop online as opposed to in store for non-essential items. If you are asked to restrict your activities and minimise your social contacts, your partner and/or other household contacts may feel burdened with additional responsibilities such as increased chores or tasks associated with looking after your other children.

In this event, please inform a member of the research team and we will guide you in accessing the appropriate services such as seeing your GP, counselling services and/or speaking with organisation such as Lifeline (13 11 14). You are welcome to contact the researchers at any time via email or phone to discuss this further and you can withdraw from the study at any stage. You will not incur any risk if you choose to withdraw.

9 What if new information arises during this research project?

There are times where during a research project, new information may become available about the condition we are investigating. If this was to occur, the researcher will inform you about it and discuss whether you would like to continue to take part in the study. If you decided that you would still like to be a part of the study, we may ask you to sign an updated consent form.

If we discover new information that leads us to believe that it would be in your best interests to withdraw from the study, the researcher will discuss the reasons with you.

10 What if I withdraw from this research project?

You can withdraw from the study at any stage. If you decide to withdraw, please let a member of the research team know via email or phone. We will discuss the reason for withdrawal with you so we can determine if there are any specific health risks or requirements linked to withdrawing.

11 Could this research project be stopped unexpectedly?

This study could be stopped unexpectedly for several reasons. For example, if we found that there were unacceptable adverse effects or new information became available regarding the effect of lockdown measures on the rate of preterm birth.

12 What happens when the research project ends?

Once the study finishes, our team will analyse the results. If you would like to be informed of the results, please let us know and we can email you a copy. Your privacy will be protected as we will only be reporting the whole group's results, which means there is no way your individual results could be traced to you.

Part 2 How is the research project being conducted?

13 What will happen to information about me?

By signing this consent form, you are consenting for authorized members of our research team to collect, store and use relevant personal information for this study. Your information may be collected from our medical records, the actigraphy device worn on your wrist and surveys that you will have completed over the duration of the study. Any information we collect with relation to this project that could identify you will be kept confidential to protect your privacy, on a secure, password protected computer system at the relevant health service. Only authorised members of the research team will have access to this information, and it will only be used for the purpose of research. This information can only be disclosed with your permission or if required to do so by law.

We anticipate that the results of this study will be published in a peer-reviewed journal and presented at various forums such as medical conferences when appropriate. Information will only be presented in a de-identified manner, which means you will not be identified, unless you give us permission. As per Monash Health research policy, we will store your information for 15 years. After this period, we may dispose of all the information in a safe and secure manner such as shredding paper records and permanently deleting any electronic records.

Information regarding your participation in this trial will be recorded in your health record.

As per Australian and/or Victorian privacy and other relevant laws, you have the right to request access to the information the research team collects and stores. You also have the right to request that any information you disagree with be rectified. If you would like to take part in our

study and would like access to the information we collect, please feel free to contact a member of the research team (their details are at the end of this document).

14 Complaints and Compensation

If you suffer from a medical condition or complication because of this trial, please contact a member of the research team immediately so that we can assist in arranging the appropriate medical treatment. Any treatment you require should be free of charge if you are a Medicare card holder and attend an Australian public hospital as a public patient.

15 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 Monash Health HREC.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2018)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

16 Further information and who to contact

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

If you want any further information concerning this project or if you develop any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor as below:

Principal Study Doctor

Name	A/Prof Daniel Rolnik
Position	Consultant Obstetrician and Gynaecologist, Monash Health
Telephone	0452 105 585
Email	daniel.rolnik@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 name	Monash Health Human Research Ethics Committee
HREC Executive Officer	HREC Executive Officer
Telephone	03 9594 4611
Email	Research@monashhealth.org

Consent Form

Title	Randomised controlled trial investigating the effect of viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women
Short Title	Viral mitigation measures and preterm birth
Project Sponsor	Monash Health
Principal Investigators	Professor Ben Mol
Associate Investigators	A/Prof Daniel Rolnik, A/Prof Atul Malhotra, Dr Shivadharshini Sridhar

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 give permission for my doctors, other health professionals, hospitals, or laboratories outside this hospital to release information to Monash Health concerning my health for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to my participation in this research project as described and understand that I am free to withdraw them at any time during the research project without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Participant's Name (please print): _____

Participant's Signature: _____ Date_____

Name of Witness*

to participant's signature (please print) _____

Signature: _____ Date: _____

* Witness is not to be the investigator, a member of the study 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 Study Doctor

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 Study Doctor

(please print): _____

Signature: _____ Date: _____

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

FORTNIGHTLY PARTICIPANT SURVEY

1. On average, how often did you wear a face covering when outside your home in a week?
    a. Never
    b. Sometimes (specify which type)
    c. Most of the time (specify which type)
    d. Always (specify which type)
2. On average, how often were you within 1.5m distance of another person who is not a household contact in a week?
    a. Never
    b. Sometimes
    c. Most of the time
    d. Always
3. On average, how often did you perform hand hygiene prior to touching your nose/mouth in a week?
    a. Never
    b. Sometime
    c. Most of the time
    d. Always
4. One average, how many times did you leave your house for activities that are not considered 'essential' in a week? Essential activities include shopping for essentials, to work/study, to give/seek care or for outside exercises.
    a. 0-5 times
    b. 5-10 times
    c. 10-20 times
    d. > 20 times
5. On average, how often did you travel beyond 5km of your place of residence in a week?
    a. 0-5 times
    b. 5-10 times
    c. 10-15 times
    d. >15 times
6. On average, how often did you leave your home between the hours of 9pm-5am for non-essential purposes in a week? Essential activities include for work/study or to seek/give care.
    a. 0-5 times
    b. 5-10 times
    c. 10-15 times
    d. >15 times
7. On average, how many visitors did you have to your home in a week, excluding an intimate partner?
    a. 0-2
    b. 2-4
    c. 4-6
    d. >6

Sleep, Mood and Quality of Life

1. How many hours of sleep are you getting each night?
    a. 2-6 hours
    b. 6-8 hours
    c. 8-10 hours
    d. >10 hours
2. How often have you felt sad/low for no good reason?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
3. How often have you felt anxious or panicky for no good reason?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
4. How often have you looked forward with enjoyment to things?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
5. How often have you felt like you were having trouble coping with things?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
6. How often have you felt that you have someone with whom you can share your joys, sorrows and anxieties with?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
7. How often have you felt that you have someone to count on when you need help?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
8. How often have you felt unable to cope with performing your usually day to day activities alongside your pregnancy?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
9. How satisfied do you feel with your social life right now?
    a. No satisfaction
    b. Some satisfaction
    c. Mostly satisfaction

d. Complete satisfaction

Study Experience (For intervention group only, included as part of the final survey)

1. How difficult do you feel it was to comply with the lockdown measures in this study?
    a. Very difficult
    b. Mostly difficult
    c. Neither difficult nor easy
    d. Mostly easy
    e. Very easy
2. Which measure was the most difficult to comply with?
    a. Maintaining 1.5m distance between yourself and another individual
    b. Wearing a face covering
    c. Performing hand hygiene prior to touching your nose/mouth
    d. Remaining withing 5km of your residence
    e. Remaining at home between 9pm-5am, except for essential purposes (work/study or to seek/give care)
    f. Only leaving home for essential purposes (work or study, to seek/give care or for outside exercise)
    g. Refraining from having visitors to your home except for an intimate partner
3. How disruptive were these lockdown measures to your day-to-day life?
    a. Very disruptive
    b. Mostly disruptive
    c. Somewhat disruptive
    d. Not disruptive at all
4. If we could definitively prove that lockdown decreased the risk of preterm birth, do you feel that this is a reasonable set of measures to ask pregnant women to comply with?
    a. Yes
    b. No
5. Do you feel that the lockdown measures you were required to comply with put a strain on your partner/friends/family?
    a. Yes (specify why/how)
    b. No
6. Was the wrist device you were asked to wear comfortable?
    a. Yes
    b. No
7. Did you feel it was reasonable to ask pregnant women to wear the wrist device for the duration of their time in the trial?
    a. Yes
    b. No
8. Were there any reasons why you felt you could not wear the device or had to remove it for extended periods of time (e.g more than 3 hours)?
    a. Yes (please specify when/why)
    b. No
9. Please feel free to add any other thoughts/comments/concerns about your experience in this study:
    a. ……..

iPREM Pilot Trial: Reporting Checklist

		Reporting Item	Page Number
Administrative information			
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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 15
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2

Roles and responsibilities: sponsor and funder	#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 – sponsor/funders did not play any roles in study design
Roles and responsibilities: committees	#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)	12, 13
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	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5, 6
Objectives	#7	Specific objectives or hypotheses	6

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, non-inferiority, exploratory)	6
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	7
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)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in	N/A - the intervention will not be modified for any given trial participant.

		response to harms, participant request, or improving / worsening disease)	
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A - as this is a feasability trial, there is no specific adherence recommendations given this is what we are measuring in the first instance.
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	9-11
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 (see Figure)	8, 9

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	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
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	7
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	7

Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A - participants and healthcare staff are not blinded. There are no circumstances under which emergency unblinding of data collectors/analysts will be required.
Methods: Data collection, management, and analysis			
Data collection plan	#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,	10, 11

		laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	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	12
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	13, 14
Statistics: outcomes	#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	11, 12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11, 12

Statistics: analysis population and missing data	#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)	11, 12
Methods:			
Monitoring			
Data monitoring: formal committee	#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	12, 13
Data monitoring: interim analysis	#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	13
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	12

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
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)	11
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
Consent or assent: ancillary studies	#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	13, 14

		confidentiality before, during, and after the trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13, 14
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	13
Dissemination policy: trial results	#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	13, 14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	14
Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A

reproducible research			

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	See supplementary material
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

Notes:

- 5c: N/A - sponsor/funders did not play any roles in study design
- 11b: N/A - the intervention will not be modified for any given trial participant.
- 11c: N/A - as this is a feasability trial, there is no specific adherence recommendations given this is what we are measuring in the first instance.
- 17b: N/A - participants and healthcare staff are not blinded. There are no circumstances under which emergency unblinding of data collectors/analysts will be required. The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 24. April 2023 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Feasibility of a pregnancy intervention mimicking viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women enrolled in antenatal clinics in Melbourne, Australia: protocol for a pilot, randomised trial

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Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Paediatrics, Infectious diseases
Keywords:	COVID-19, NEONATOLOGY, OBSTETRICS

PROTOCOL PAPER

Long Title: Feasibility of a pregnancy intervention mimicking viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women enrolled in antenatal clinics in Melbourne, Australia: protocol for a pilot, randomised trial

Short Title: iPREM Pilot (Isolate to Prevent pretERM birth)

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ABSTRACT

Introduction: Preterm birth is a leading cause of perinatal morbidity and mortality. During the COVID-19 pandemic, reduction in rates of preterm birth in women exposed to viral mitigation measures was reported by multiple studies. In addition, others and we observed a more pronounced reduction of preterm birth in women who had previously experienced a preterm birth. The aim of this pilot study is to establish the feasibility of a lifestyle intervention based on viral mitigation measures in high-risk pregnancies, with the ultimate aim to reduce the incidence of preterm birth.

Methods and Analysis: One hundred pregnant women, enrolled in antenatal clinics at two tertiary maternity centres in Melbourne, Australia, who have had a previous preterm birth between 22-34 weeks gestation will be recruited. This is a two-arm, parallel group, open-label randomised controlled feasibility trial: fifty women will be randomised to the intervention group, where they will be requested to comply with a set of lifestyle changes (similar to the viral mitigation measures observed during the pandemic). Another fifty women will be randomised to the control group, where they will undergo standard pregnancy care. The primary outcome of this trial is feasibility, which will be assessed by measuring patient eligibility rate, recruitment rate, compliance rate and data completion rate. Secondary outcomes include incidence of preterm birth, maternal satisfaction, maternal quality of life and other pregnancy outcomes. Standard methods in statistical analysis for randomised controlled trials on an intention to treat basis will be followed.

Ethics and Dissemination: This trial has been approved by the Monash Human Research Ethics Committee; approval reference number RES-22-0000-122A. Study findings will be reported and submitted to peer-reviewed journals for publication, and presentation at conferences.

Trial Registration Number:

ACTRN12622000753752; pre-results

ARTICLE SUMMARY

Strengths and Limitations of the Study

- This study is the first randomised controlled trial to investigate the feasibility of a pregnancy intervention that mimics viral mitigation measures on preterm birth rates.
- Outcomes are measured using both subjective (surveys) and objective (actigraphy device data) measures to provide a comprehensive range of data regarding acceptability of the intervention.
- Compliance to the intervention is self-reported.
- Due to the nature of the intervention, it is not possible to blind patients or clinicians involved in the recruitment process.

INTRODUCTION

Preterm birth, defined as delivery prior to 37 weeks gestation, is the leading cause of perinatal morbidity and mortality worldwide. Globally, approximately 15 million preterm births occur yearly and more than 1 million babies die shortly after birth as a direct result of their prematurity.(1) In Australia, 8.6% of deliveries are preterm with the average gestational age at birth being 33 weeks.(2) Preterm delivery occurs after the following obstetric precursors: spontaneous preterm labour (40-45%), preterm premature rupture of membranes (PPROM, 25-30%) or where delivery is indicated due to maternal or fetal compromise (30-35%).(3) An increasing degree of prematurity is known to correlate with a greater risk of complications including neurodevelopmental delay, cerebral palsy and cardio-respiratory disease.(4) Prematurity also has a significant economic impact; 72% of preterm infants will need admission to the neonatal intensive care unit where the average length of admission is 28 days and the cost per day is almost $2000.(2, 5) Mothers of preterm infants take longer to return to work, have a lower medium income and increased out of pocket healthcare costs. (6)

The exact causality of preterm birth remains unknown, however risk factors include previous preterm birth, maternal age, smoking, multiple gestation, gestational diabetes, maternal literacy level and social disadvantage.(3) Although we have methods to manage high risk women including progesterone treatments, aspirin and cervical cerclage, overall preterm birth rates have continued to rise in most industrialised nations. (7, 8)

The outbreak of COVID-19 brought the world to a standstill, having drastic social and economic impacts. The first Australian case was detected in Victoria in January 2020 and by March, measures including social distancing, wearing face masks and performing hand hygiene were introduced to mitigate virus spread.(9) Unexpectedly, it has been observed around the world that pregnant women exposed to mitigation measures for the COVID-19 virus have had a reduction in preterm birth rates by 20-30%, with this effect being more pronounced in early preterm birth (<34 weeks).(10-12) At Monash Health in Melbourne, an observational study demonstrated a 30% reduction in preterm birth rate prior to 34 weeks (risk ratio (RR) 0.74 (95% CI, 0.57-0.96; p = 0.021). This effect was stronger in women who had experienced a previous preterm birth (RR 0.42, 95% CI 0.21-0.82; p = 0.008) when compared to parous women who had not experienced a preterm birth (RR 0.93, 95% CI 0.63-1.28; p = 0.714).(13)

We hypothesise that in women with a previous preterm birth (<34 weeks), a pregnancy intervention mimicking COVID-19 mitigation measures will reduce the incidence of a subsequent preterm birth. We propose that the mechanism of action behind this effect may be due to a reduction in physical activity, stress, noise or air pollution, medical interventions and/or reduced rates of infection.

While observational studies, including those conducted by our team, have demonstrated that COVID-19 mitigation measures have an effect on preterm birth rates, these findings are inconsistent, it is unclear which aspect of these measures contribute to the phenomenon, and there have been no randomised controlled trials that have further investigated this effect to establish causality. We believe that we have a unique opportunity to study this effect further as we are based in Melbourne, where the population has been subject to some of the harshest lockdowns. However, we must first assess feasibility of such an intervention in pregnancy prior to conducting any larger randomised trials.

AIM

The aim of this study is to investigate the feasibility of a lifestyle intervention in pregnancy that mimics viral mitigation measures in pregnant women who have previously had a preterm birth between 22-34 weeks.

METHODS AND ANALYSIS

Study Design

This is a multi-site, two-arm open-label randomised controlled clinical trial that will be conducted across tertiary maternity centres in Melbourne, Australia. The Standard Protocol Items: Recommendations for Interventional Trials checklist was used to prepare this report.(14) The flowchart of the study design is shown in Figure 1. The flowchart of the study design is shown in Figure 1. This trial was registered with the Australia New Zealand Clinical Trials Registry on 26th May 2022 (Table 1).

Data Category	Information
Primary registry and trial identifying number	Australian New Zealand Clinical Trials Registry ACTRN12622000753752
Date registered	26 May, 2022
Source(s) of monetary or material support	Monash Health Monash University
Primary Sponsor	Monash Health
Secondary Sponsor	Monash University
Contact for Public and Scientific Queries	Associate Professor Atul Malhotra Email: atul.malhotra@monash.edu
Public Title	iPREM Pilot (Isolate to Prevent pretERM birth)
Scientific Title	Feasibility of a pregnancy intervention mimicking viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women enrolled in antenatal clinics in Melbourne, Australia: protocol for a pilot, feasibility randomised trial
Countries of Recruitment	Australia
Health condition(s) studied	Premature birth
Intervention(s)	Active comparator: Pregnancy intervention mimicking COVID-19 viral mitigation measures
	Control comparator: Standard pregnancy care
Key inclusion and exclusion criteria	Inclusion: Pregnant women ≥18 years, previous preterm birth between 22-34 weeks gestation
	Exclusion criteria: Fetus with major congenital abnormality
Study Type	Interventional
	Allocation: randomized interventional model
	Primary purpose: feasibility
Date of first enrolment	July 2022
Target sample size	100
Recruitment status	Recruiting
Primary Outcome (s)	Feasibility

Secondary Outcome(s)	Preterm birth < 34 weeks, maternal quality of life and satisfaction and other pregnancy outcomes

Table 1: Trial Registration Data

Sample Size

Given the primary objective of this trial is to establish feasibility, we aim to recruit up to one hundred pregnant women, fifty of whom will be randomised to the intervention group and fifty of whom will be randomised to the control group. We chose this sample size as we estimated that at our initial recruitment site, there may approximately 150-200 eligible women and so a sample size of one hundred (i.e. half of the eligible population) would be representative of the overall group.

Patient Population

Adult pregnant women receiving care at antenatal clinics who are at 'high risk' for having a preterm birth, where 'high risk' will be defined as having had a previous preterm birth between 22-34 weeks gestation.

Inclusion Criteria

Pregnant women, singleton or multiple gestation, will be eligible for this trial if they are aged 18 years or over and have previously delivered a preterm baby between 22+0 and 34+0 gestation, either spontaneously or iatrogenically. Women must primarily speak English and have the ability to read and write.

Exclusion Criteria

Pregnant women will be excluded if they are carrying a fetus with one or more major congenital abnormalities.

Recruitment

Pregnant women who are enrolled in each recruitment site's antenatal clinics will be screened by a clinical team who are familiar with the eligibility criteria. We will make an entry onto the relevant medical records system flagging eligible women. We will also brief clinicians in the clinic on the study details so that they can refer any eligible patients we may have missed in our initial screening process. Additionally, we will display flyers advertising the study in clinic rooms so women who feel they are eligible can contact the

research team themselves. When an eligible woman presents to the clinic, we will ask her treating clinician to briefly explain the study and provide her with a patient invitation form. A member of our research team will then approach eligible patients and explain trial details prior to recruitment. Prospective participants will be given 48 hours to consider whether they would like to take part in the trial. If the patient agrees to participate in the trial, they will be asked to sign a written consent form. We will ensure to obtain and store an individual record of all non-recruited patients, including their reasons for exclusion.

No members of the research team will be involved in the care of potential participants at the site of recruitment, ensuring that there are no unequal or dependent relationships. This study will not be blinded to participants as well as nurses, midwives, doctors, or investigators who are involved in the recruitment process. The investigator collecting study outcome data once a participant has completed the trial and the investigator who analyses the data will be blinded to the group to which participants were allocated.

Recruitment commenced in June 2022 and is expected to take around 18-24 months for completion.

Randomisation

Pregnant women who are successfully recruited are randomised and allocated on the first day of the trial using Research Electronic Data Capture (REDCap, Version 12.4.10, Vanderbilt University) by a member of the research team. REDCap is a secure, web-based data collection and management software that meets Health Insurance Portability and Accountability Act (HIPAA) compliance standards.(15, 16) The randomisation table was generated by using the statistical software Stata, with variable block sizes of 2 and 4.(17)

Interventions

Intervention Group

This pregnancy intervention is designed to mimic the stage 3 and 4 COVID-19 virus mitigation measures implemented in metropolitan Melbourne, Australia in 2020-21. Briefly, this involved social distancing, restrictions to movements outside the home unless necessary, imposition of a curfew as well as hygiene recommendations including hand hygiene and mask wearing.(9) Originally, alongside their standard pregnancy care, study

participants were asked to comply with the following measures for the duration of the intervention.

1. Refrain from leaving their homes unless required to do so, such as shopping for essentials, to work or study, to seek or give care, for safety purposes (e.g. escaping domestic violence) or for outside exercise.
2. Avoid having visitors to their home unless it is their intimate partner and try to maintain social distancing where possible, that is, a 1.5m distance between themselves and another party unless in their own home or with an intimate partner.
3. Wear a face mask or covering when outside their home and perform hand hygiene prior to removing their mask or touching any aspect of their nose or mouth.
4. Aim to remain at home between 9 pm and 5 am unless they are required to leave for work or study or to seek or give care and avoid travelling beyond 5km of their place of residence except for essential reasons.

Initial recruitment rates were approximately 30%, i.e 30% of eligible participants consented to take part in the trial and the majority of eligible participants who declined to take part did so as they felt that the intervention was too strict. In order to increase recruitment, the research team made the decision to relax the requirements of the intervention. As of now, participants who are assigned to the intervention group will be asked to comply with the following:

1. Try to minimise the number of visitors to their home and refrain from attending large social gatherings where possible.
2. Remain in their homes unless required to do so, such as for study/work, shopping for essentials, to seek/give care, for outdoor exercise or if their home environment becomes unsafe in any way (e.g domestic violence).
3. Wear a face mask/covering when outside their home and perform hand hygiene prior to removing their mask/touching any aspect of their nose or mouth.

Standard pregnancy care will be defined as routine antenatal care appointments, ultrasound scans, pathology and any other investigations or treatments required as determined by the participant's antenatal care team.

Control Group

Participants randomised to the control group will undergo standard pregnancy care without any restrictions.

Participants will begin the trial intervention two weeks prior to the gestational age at which the study participant's previous preterm birth occurred (i.e., if they delivered in their previous pregnancy at 32^{+3} weeks, their first day in the trial will be at 30^{+3} weeks). If the participant has had multiple preterm births, they will begin the trial 2 weeks prior to the gestational age of their earliest preterm delivery. The maximum gestation for recruitment will be 31 weeks to ensure that the participant is in the trial for at least 3 weeks. Therefore, if they previously gave birth at 33^{+6} weeks gestation, they will be required to begin the study at 31 weeks gestation. The duration of the intervention will be six weeks (i.e., two weeks prior and four weeks post the gestational age of the previous preterm birth) or until 34 weeks gestation or until birth, whichever comes first.

All participants will be required to complete short, online surveys (which will be developed and distributed to their email via REDCap) to assess their hygiene, social contacts, activities, mood and quality of life at baseline and then on a fortnightly basis for the duration of their time in the trial (see supplementary material).

All participants will also be encouraged to wear an actigraphy device (provided by the study team), similar to a watch, on their non-dominant wrist, 24 hours a day, for the duration of their time in the trial. For the purposes of this study, we have chosen the GENEActiv Original (Activinsights, Kimbolton, United Kingdom). It is a 43x40x13mm water resistant device, which has an inbuilt tri-axial piezoelectric accelerometer, light intensity and temperature sensors. The device will be set to record data at a sampling rate frequency of 20Hz. As sampling rate has a direct impact on the actigraph's battery life, this will enable the participant to wear the device for four weeks without requiring a re-charge. We will configure the device to automatically start recording on the participant's first day in the trial so they will not be required to push any buttons. If the participant remains in the trial for greater than four weeks, a research assistant will collect the old device from them and provide them with a new, charged device. Once the participant has finished their time in the trial, raw data will be downloaded from the devices using the GENEActiv PC Software (Version 3.3, Activinsights) as a '.bin' file and analysed.

Patient and Public Involvement

The study team consulted patients and clinicians at the antenatal clinic where recruitment is taking place for their advice and input into the design of the study.

OUTCOMES

Primary Outcome

Feasibility

We will measure feasibility using the following criteria:

Patient eligibility rate, which will be measured as the proportion of eligible women screened at the antenatal clinic who are expected to consent to taking part in this trial. We have set a pre-defined target of 50%.

Patient recruitment rate, which will be measured as the proportion of eligible women that consent to taking part in the study who are randomised (noting that there may be a significant time period between consent and randomisation). We have set a pre-defined target of 50%.

Compliance rate, which will be measured as the proportion of participants in the intervention group who are considered to have good compliance with the intervention. This will be measured via fortnightly, participant filled surveys and we will set a pre-defined target of 75%. On each fortnightly survey, participants will be asked questions pertaining to their compliance with each restriction measure. For example, participants will be asked how often they wore a mask when outside their home and if they were to answer either 'most of the time' or 'all of the time', we would classify this as having $\geq$ 75% compliance with this restriction measure. Participants must report $\geq$ 75% compliance for all restriction measures in order to be defined has having 'good compliance' with the intervention. This will be measured at the end of the trial.

Data completion rate, which will be measured as the proportion of trial participants who complete the final survey (i.e., the survey that the participant is required to complete once they reach an endpoint). This will be measured at the end of the trial. We have set a pre-defined target of $\geq$ 75%.

Secondary Outcomes

Secondary outcomes will include incidence of preterm birth prior to 34 weeks gestation, maternal satisfaction, and quality of life as well as other pregnancy outcomes such as pregnancy duration, incidence of stillbirth and incidence of iatrogenic or spontaneous delivery. We will measure maternal satisfaction and quality of life via fortnightly surveys we have developed based on previously validated questionnaires including but not limited to the Beck Depression Inventory, QOL-GRAV and Multidimensional Scale of Perceived Social Support. We will also collect non-dominant wrist raw acceleration data through the actigraphy device. The raw acceleration data will be used to derive physical activity patterns, estimate sleep-wake cycle and verify the compliance with wearing the device.

Other data to be collected

Demographic data collected will include maternal demographic data such as birth country, age, marital status, medical history, drug use, risk factors for preterm birth, gravida/parity, obstetric history, details of current pregnancy, incidence of prelabour premature rupture of membranes, incidence of presumed chorioamnionitis, use of antenatal steroids, mode of delivery and maternal death. We will also collect infant demographic data such as birthweight in grams.

Other neonatal outcomes collected will include incidence of admission to neonatal intensive care (NICU) or special care nursery (SCN), incidence of NICU stay >48 hours, neonatal morbidity (5-minute Apgar score <5, respiratory distress syndrome requiring intubation, grade 3 or 4 intraventricular haemorrhage, neonatal seizures, culture-positive neonatal sepsis, retinopathy of prematurity requiring treatment, necrotising enterocolitis) and neonatal death.

A member of the research team will download data from the actigraphy device from the device after the participant has completed their time in the trial. Once the participant has given birth, secondary and other data will be collected by a member of the research team who is blinded to participant's allocation.

DATA ANALYSIS

We will use the open-source package GENEActiv and GENEA In R (GGIR, Version 2.5) to translate raw actigraphy data to readable information.(18) Data will be downloaded from

each device as a .bin file, which will be read and translated to a .csv file by the GGIR package according to predefined parameters. Initially, GGIR will perform sensor calibration in the data collected to check and correct calibration errors in the accelerometer(19). Due to the raw data size, we will set GGIR to summarise the collected 20 Hz sample-rate data to 5s epochs.

Feasibility targets will be assessed first. Baseline continuous covariates will be expressed as mean and standard deviation or median and interquartile range depending on the distribution of the data as assessed by inspection of histograms and quantile-quantile (QQ) plots. Normally distributed continuous variables will be compared between the groups using independent-samples t-test, and non-normally distributed variables will be compared between the trial arms with the Wilcoxon rank-sum test.

Categorical variables will be expressed as counts and percentages and compared between the study groups using the Chi-squared test or Fisher's exact test, as appropriate. Descriptive statistics will be reported for assessment of feasibility as previously defined in the study outcomes section.

The effect of the intervention on the odds of preterm birth and other binary pregnancy outcomes will be modelled using univariable logistic regression models and expressed as the odds ratio with 95% confidence intervals. Multivariable models will be used to adjust for covariates with significant imbalances between the groups at baseline, if needed. Analyses will be performed according to an intention-to-treat principle, and secondary per protocol analysis will be performed including only participants from the intervention group with compliance ≥ 75%.

All statistical analyses will be conducted in the statistical environment R, and p-values below 0.05 will be considered statistically significant. We will report findings in accordance with Consolidated Standards of Reporting Trials guidelines.

ADVERSE EVENTS

Serious Adverse Events (SAE)

SAEs will be defined as any event required admission to hospital (excluding admission for delivery), maternal or fetal death, fetal malformations, any event that leads to maternal

disability and any event where a participant contacts the study team with concerns regarding a serious deterioration in their mental health during the trial.

Adverse Events (AE)

Any other event reported by a participant or their partner not needing hospital admission or not falling in a category of SAEs.

DATA SAFETY MONITORING BOARD (DSMB)

An independent DSMB comprising of a senior research fellow in obstetrics and gynaecology, a consultant neonatologist and a perinatal epidemiologist has been formed to review the study, the data generated and ensure safety of all participants. Members of the DSMB do not have a vested financial, scientific, or other conflict of interest with this trial. All SAEs will be reported to the data safety monitoring board (DSMB) within 24-48 hours of the team becoming aware of the event.

An interim analysis evaluating the safety of the trial will be conducted after fifty eligible women have been screened. The DSMB will be required to evaluate any adverse events and assess the ongoing safety of the trial. They will have the ability to suspend or terminate the study if required on the basis of a lack of feasibility or any SAEs observed. Given the feasibility nature of the trial and that the interim analysis will only assess safety, no sequential trial adjustments to the alpha level will be made.

REPORTS TO HUMAN RESEARCH ETHICS COMMITTEE (HREC)

Any SAEs that the DSMB deem will necessitate a temporary halt of the trial pending review and any changes to the protocol or patient information consent form (PICF) will be reported to the HREC. We will also ensure to provide an interim report following the recruitment of fifty participants to the trial as well as an annual research progress report.

ETHICS AND DISSEMINATION

Ethics

This study has been approved by the Monash Health Human Research Ethics Committee and will be conducted in accordance with the approved protocol/amendment(s) and NHMRC National Statement on Ethical Conduct in Human Research 2007 (updated 2018). The study will also comply with the Declaration of Helsinki and with the Good Clinical Practice (GCP) standards. An expert team of senior obstetricians, neonatologists,

researchers and psychiatrists were consulted regarding the intervention and protecting the psychological safety of the women in the trial. We have ensured that participants have ample opportunity to contact the study team if they are concerned and have developed the surveys in consultation with a psychiatrist to appropriately assess the quality of life of trial participants.

Data for this trial will be collected from electronical medical records system, surveys completed by participants and from actigraphs utilised by participants following informed consent. Each participant will be assigned a unique participant identifier which will be the only number that appears on their reports to maintain confidentiality. Only authorised members of the research team will be able to log into the secure web-based portal, REDCap, to input trial data for each participant using their unique participant identifier. De-identified actigraph device data will be stored in a password protected computer file, also only accessible to authorized members of the research team. All data will be stored for 15 years after which it will be disposed of via permanent deletion.

Consent

Informed, written consent will be obtained using a specifically designed PICF (see supplementary material) from potential participants after a member of the research team has ensured that the participant understands the study procedures involved, the potential benefits and/or risks as well as the expected duration of the intervention. Participants will be made aware that their participation is entirely voluntary and that they are free to withdraw at any stage for any reason. The research team member will also inform participants that withdrawal of consent will not affect their relationship with their physician or their right to appropriate medical treatment.

Dissemination

The study results will be disseminated by publication in peer-reviewed journals and presented at conferences as appropriate.

OTHER

Author Contributions: The initial concept was developed by AM, DLR and BWM. All authors contributed to the design of the study. Shivadharshini S drafted the ethics application, protocol, case report forms, surveys and manuscript. AM, DLR, BWM, RCP, RTS, FB-J, DM and JS made critical revisions and assisted with ethics application submission, editing of protocol and editing of manuscript. All authors have read and approved the final manuscript and are accountable for its accuracy.

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Competing Interests: None declared

Patient Consent for Publication: Not required

Provenance and Peer Review: Not commissioned; externally peer reviewed.

REFERENCES

1. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller A-B, et al. Born Too Soon: The global epidemiology of 15 million preterm births. Reproductive Health. 2013;10(1):S2.
2. Welfare AIoHa. Australia's Mothers and Babies 2016 - in brief. Perinatal Statistics Series. Canberra: Australian Institute of Health and Welfare; 2018.
3. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. The Lancet. 2008;371(9606):75-84.
4. Organization WH. Born Too Soon. The Global Action Report on Preterm Birth. Geneva: World Health Organization; 2012.
5. Zainal H, Dahlui M, Soelar SA, Su TT. Cost of preterm birth during initial hospitalization: A care provider's perspective. PloS one. 2019;14(6):e0211997-e.
6. Fox H, Callander E. Cost of preterm birth to Australian mothers: Assessing the financial impact of a birth outcome with an increasing prevalence. Journal of Paediatrics and Child Health. 2021;57(5):618-25.
7. Chawanpaiboon S, Vogel JP, Moller A-B, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. The Lancet Global Health. 2019;7(1):e37-e46.
8. Newnham JP, Dickinson JE, Hart RJ, Pennell CE, Arrese CA, Keelan JA. Strategies to prevent preterm birth. Frontiers in immunology. 2014;5:584-.
9. Storen RC, N. COVID-19: a chronology of state and territory government announcements (up until 30 June 2020). In: Services P, editor. Canberra: Parliamentary Library 2020.
10. Philip RK, Purtill H, Reidy E, Daly M, Imcha M, McGrath D, et al. Unprecedented reduction in births of very low birthweight (VLBW) and extremely low birthweight (ELBW) infants during the COVID-19 lockdown in Ireland: a 'natural experiment' allowing analysis of data from the prior two decades. BMJ Global Health. 2020;5(9):e003075.
11. Been JV, Burgos Ochoa L, Bertens LCM, Schoenmakers S, Steegers EAP, Reiss IKM. Impact of COVID-19 mitigation measures on the incidence of preterm birth: a national quasi-experimental study. The Lancet Public Health. 2020;5(11):e604-e11.
12. Matheson A, McGannon CJ, Malhotra A, Palmer KR, Stewart AE, Wallace EM, et al. Prematurity Rates During the Coronavirus Disease 2019 (COVID-19) Pandemic Lockdown in Melbourne, Australia. Obstetrics & Gynecology. 2021;137(3).
13. Rolnik DL, Matheson A, Liu Y, Chu S, McGannon C, Mulcahy B, et al. Impact of COVID-19 pandemic restrictions on pregnancy duration and outcome in Melbourne, Australia. Ultrasound in Obstetrics & Gynecology. 2021;58(5):677-87.
14. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Annals of internal medicine. 2013;158(3):200-7.
15. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.
16. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
17. StataCorp. Stata Statistical Software: Release 17. 17 ed. College Station, TX: StataCorp LLC; 2021.
18. Migueles JH, Rowlands AV, Huber F, Sabia S, van Hees VT. GGIR: A Research Community–Driven Open Source R Package for Generating Physical Activity and Sleep

Outcomes From Multi-Day Raw Accelerometer Data. Journal for the Measurement of Physical Behaviour. 2019;2(3):188-96.
19. Hees VTv, Fang Z, Langford J, Assah F, Mohammad A, Silva ICMd, et al. Autocalibration of accelerometer data for free-living physical activity assessment using local gravity and temperature: an evaluation on four continents. Journal of Applied Physiology. 2014;117(7):738-44.

FIGURE LEGEND

Figure 1 – Flow Chart.

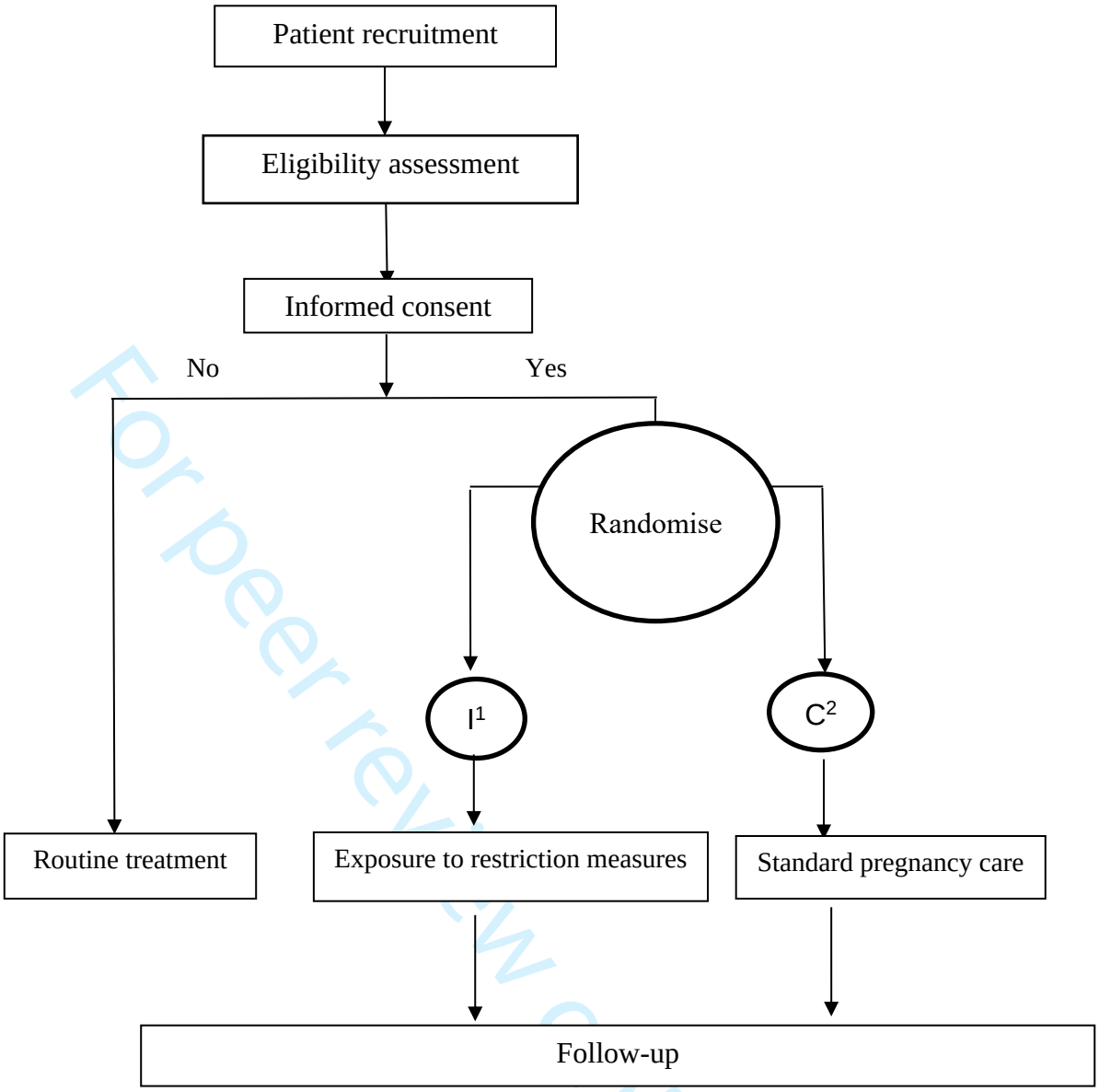

Figure 1. Flowchart.

1 Intervention

2 Control

Effect of viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women: protocol for a pilot, feasibility randomised trial

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SUPPLEMENTARY MATERIAL

PARTICIPANT INFORMATION AND CONSENT FORM (MASTER)

Title	Randomised controlled trial investigating the effect of viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women
Short Title	iPREM (Pilot)
Project Sponsor	Monash Health
Principal Investigator(s)	Professor Ben Mol
Associate Investigator(s)	Dr A/Prof Daniel Rolnik A/Prof Atul Malhotra Dr Shivadharshini Sridhar

Part 1 What does the participation involve?

1 Introduction

We are inviting you to take part in this research project because you are currently pregnant and have previously given birth to a preterm baby (i.e. a baby born between 22 and 34 weeks of gestation). Your information was obtained from our medical records system.This research project is investigating the feasibility and safety of an intervention in pregnancy that may decrease the risk of preterm birth.

This participant information and consent form will explain the purpose of our project and what it will involve as clearly as possible so that you can be fully informed before you decide whether you would like to take part.

Please take your time to read through this statement carefully. If you have any questions or concerns, please do not hesitate to contact our researcher via email or phone. Before deciding whether you would like to participate, you may want to talk about it with a family member or a medical professional.

Participation in this research project is voluntary and if you decide you do not wish to take part, you do not have to. You will still receive the best possible care regardless of whether you are involved with our study.

If you do decide to take part, you will need to sign the consent section. By signing this, you are telling us that:

- You understand everything you have read in this statement
- You consent to your participation in this project
- You consent to the use of your personal and health information as described

You will be given a copy of this participant information and consent form to keep.

2 What is the purpose of this research?

Preterm birth (i.e. when a baby is born too early) occurs in around 9% of all deliveries in Australia and can be associated with significant medical consequences for babies. During the COVID-19 pandemic, we, and many other groups around the world have observed that women who have been pregnant during lockdown have experienced a decreased rate of preterm birth. At Monash Health, a 30% decrease in women giving birth before 34 weeks of gestation was observed and this effect was stronger in women who had a previous preterm birth. We believe that this phenomenon may have to do with changes in the way we lived during lockdowns - physical distancing, changes in physical activity, work from home and possibly improved hygiene.

The purpose of this study is to investigate whether it is feasible to conduct an intervention in pregnancy that mimics the COVID-19 lockdowns and observe if there is an associated decrease in the rate of preterm birth in women who have previously experienced a preterm birth. Once we can establish feasibility and safety of this intervention, larger studies may be conducted to further establish whether these measures actually decrease preterm birth rates.

This research has been initiated by a research team led by Professor Ben Mol. This team, alongside the associate investigators listed above have experience looking after pregnant women and premature babies.

3 Who is organising and funding the research?

This research project is being conducted and led by Professor Ben Mol and his research team.

4 What does participation in this research involve?

If we determine that you are eligible to participate and you choose to take part in this study, you will be required to sign the consent form below.

We are inviting 100 women to take part in this study. 50 women will be randomly assigned to the 'control' group and undergo standard pregnancy care with no changes. 50 women will be randomised to the 'intervention' group, where they will be asked to comply with a pregnancy intervention that mimics the lockdown measures implemented in Melbourne to prevent the transmission of COVID-19.

If you are part of the pregnancy intervention group, you will be asked to try and comply with the following measures to the best of your ability for the duration of the study:

- Refrain from attending social gatherings and maintain 1.5m distance between yourself and another individual when outside your home
- Try to wear a face mask or covering whenever you leave your home
- Try to perform hand hygiene prior to touching your nose or mouth
- Try to remain in your home unless you must leave for study/work, for essential services, to seek**,** safety purposes (e.g you do not feel safe in your home) or give care or to do outdoor exercise
- Try to remain at home between the hours of 9pm-5am unless you must leave for work/study**,** safety purposes or to seek/give care
- Avoid having visitors to your home unless they are an intimate partner
- Try not to travel beyond 5km from your place of residence

We understand that there may be certain circumstances that mean you cannot follow through with all the above recommendations, for example, important events that you must attend such as a wedding or funeral. You are of course free to attend at your discretion, we just ask that wherever you can, please try to follow the recommendations as much as possible. For instance, if you attend a wedding, consider following at least some of the recommendations such as wearing a facemask and performing hand hygiene.

The study will begin 2 weeks before the gestation at which you gave birth to your previous preterm baby (i.e. if you gave birth at 32 weeks, the study would begin at 30 weeks gestation of your current pregnancy). However, if your previous preterm baby was born at 33+6 weeks gestation, the study will begin at 30+6 weeks gestation of this pregnancy so that you are in the study for at least 3 weeks. It will be conducted for 6 weeks (i.e. 2 weeks before and 4 weeks after the gestational age of your previous preterm birth), until 34 weeks gestation or until birth – whichever comes first.

You will be asked to complete a 5-10 minute fortnightly surveys over the course of the study about your work, household contacts, physical activity, hygiene practices, mood and quality of life. You will also be asked to wear a device on your wrist (figure 1), similar to a watch, that will record physical activity, temperature, light and sleep for the duration of your time in the study.

Figure 1. Actigraphy device.

You will not be paid to take part in this research project and there will be no additional costs to you associated with your participation.

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

Participation in this trial is entirely voluntary and if you do not wish to take part you are in no way obligated to. If you decide to take part and then change your mind, you are free to withdraw at any stage – you can easily do this by contacting the researcher via email or phone and informing them of your wish to withdraw.

If you do decide to take part, you will be given a copy of this patient information consent form to sign and a copy to keep.

Your decision to take part, or not take part in this study will not affect your relationship with your doctors, midwives, or the health service, and will not impact the care that you are given.

6 What are the alternatives to participation?

You do not have to take part in this study to receive treatment at this hospital. Your routine pregnancy care will not change or be impacted if you decide not to take part.

7 What are the possible benefits of taking part?

This research may provide us with further insight into prevention of preterm birth and could play an integral role in changing future clinical practice. We are conducting this study to mainly check whether such a pregnancy intervention is feasible and safe, and we are not yet sure if/which aspect of lockdown measures impact preterm birth rates. As such, there may be no clear benefit for your pregnancy from your participation.

Given the COVID-19 pandemic is still ongoing, a potential benefit for anyone who is in the intervention group of the study is that they may be less likely to contract the virus given they will be adhering to established viral mitigation measures, that is, restrictions to travel/social distancing/physical contact and recommendations regarding hygiene/face coverings known to prevent transmission.

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

We anticipate that the main risks associated with participating in this study are feelings of social isolation and perhaps decreased social support in those who are a part of the pregnancy intervention group. You may also find that the additional restrictive measures imposed may make it more difficult to perform your routine tasks, for example, you may have to shop online as opposed to in store for non-essential items. If you are asked to restrict your activities and minimise your social contacts, your partner and/or other household contacts may feel burdened with additional responsibilities such as increased chores or tasks associated with looking after your other children.

In this event, please inform a member of the research team and we will guide you in accessing the appropriate services such as seeing your GP, counselling services and/or speaking with organisation such as Lifeline (13 11 14). You are welcome to contact the researchers at any time via email or phone to discuss this further and you can withdraw from the study at any stage. You will not incur any risk if you choose to withdraw.

9 What if new information arises during this research project?

There are times where during a research project, new information may become available about the condition we are investigating. If this was to occur, the researcher will inform you about it and discuss whether you would like to continue to take part in the study. If you decided that you would still like to be a part of the study, we may ask you to sign an updated consent form.

If we discover new information that leads us to believe that it would be in your best interests to withdraw from the study, the researcher will discuss the reasons with you.

10 What if I withdraw from this research project?

You can withdraw from the study at any stage. If you decide to withdraw, please let a member of the research team know via email or phone. We will discuss the reason for withdrawal with you so we can determine if there are any specific health risks or requirements linked to withdrawing.

11 Could this research project be stopped unexpectedly?

This study could be stopped unexpectedly for several reasons. For example, if we found that there were unacceptable adverse effects or new information became available regarding the effect of lockdown measures on the rate of preterm birth.

12 What happens when the research project ends?

Once the study finishes, our team will analyse the results. If you would like to be informed of the results, please let us know and we can email you a copy. Your privacy will be protected as we will only be reporting the whole group's results, which means there is no way your individual results could be traced to you.

Part 2 How is the research project being conducted?

13 What will happen to information about me?

By signing this consent form, you are consenting for authorized members of our research team to collect, store and use relevant personal information for this study. Your information may be collected from our medical records, the actigraphy device worn on your wrist and surveys that you will have completed over the duration of the study. Any information we collect with relation to this project that could identify you will be kept confidential to protect your privacy, on a secure, password protected computer system at the relevant health service. Only authorised members of the research team will have access to this information, and it will only be used for the purpose of research. This information can only be disclosed with your permission or if required to do so by law.

We anticipate that the results of this study will be published in a peer-reviewed journal and presented at various forums such as medical conferences when appropriate. Information will only be presented in a de-identified manner, which means you will not be identified, unless you give us permission. As per Monash Health research policy, we will store your information for 15 years. After this period, we may dispose of all the information in a safe and secure manner such as shredding paper records and permanently deleting any electronic records.

Information regarding your participation in this trial will be recorded in your health record.

As per Australian and/or Victorian privacy and other relevant laws, you have the right to request access to the information the research team collects and stores. You also have the right to request that any information you disagree with be rectified. If you would like to take part in our study and would like access to the information we collect, please feel free to contact a member of the research team (their details are at the end of this document).

14 Complaints and Compensation

If you suffer from a medical condition or complication because of this trial, please contact a member of the research team immediately so that we can assist in arranging the appropriate medical treatment. Any treatment you require should be free of charge if you are a Medicare card holder and attend an Australian public hospital as a public patient.

15 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 Monash Health HREC.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2018)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

16 Further information and who to contact

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

If you want any further information concerning this project or if you develop any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor as below:

Principal Study Doctor

Name	A/Prof Daniel Rolnik
Position	Consultant Obstetrician and Gynaecologist, Monash Health
Telephone	0452 105 585
Email	daniel.rolnik@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 name	Monash Health Human Research Ethics Committee
HREC Executive Officer	HREC Executive Officer
Telephone	03 9594 4611
Email	Research@monashhealth.org

Consent Form

Title	Randomised controlled trial investigating the effect of viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women
Short Title	Viral mitigation measures and preterm birth
Project Sponsor	Monash Health
Principal Investigators	Professor Ben Mol
Associate Investigators	A/Prof Daniel Rolnik, A/Prof Atul Malhotra, Dr Shivadharshini Sridhar

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 give permission for my doctors, other health professionals, hospitals, or laboratories outside this hospital to release information to Monash Health concerning my health for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to my participation in this research project as described and understand that I am free to withdraw them at any time during the research project without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Participant's Name (please print): _____

Participant's Signature: _____ Date_____

Name of Witness*

to participant's signature (please print) _____

Signature: _____ Date: _____

* Witness is not to be the investigator, a member of the study 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 Study Doctor

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 Study Doctor

(please print): _____

Signature: _____ Date: _____

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

FORTNIGHTLY PARTICIPANT SURVEY

1. On average, how often did you wear a face covering when outside your home in a week?
    a. Never
    b. Sometimes (specify which type)
    c. Most of the time (specify which type)
    d. Always (specify which type)
2. On average, how often were you within 1.5m distance of another person who is not a household contact in a week?
    a. Never
    b. Sometimes
    c. Most of the time
    d. Always
3. On average, how often did you perform hand hygiene prior to touching your nose/mouth in a week?
    a. Never
    b. Sometime
    c. Most of the time
    d. Always
4. One average, how many times did you leave your house for activities that are not considered 'essential' in a week? Essential activities include shopping for essentials, to work/study, to give/seek care or for outside exercises.
    a. 0-5 times
    b. 5-10 times
    c. 10-20 times
    d. > 20 times
5. On average, how often did you travel beyond 5km of your place of residence in a week?
    a. 0-5 times
    b. 5-10 times
    c. 10-15 times
    d. >15 times
6. On average, how often did you leave your home between the hours of 9pm-5am for non-essential purposes in a week? Essential activities include for work/study or to seek/give care.
    a. 0-5 times
    b. 5-10 times
    c. 10-15 times
    d. >15 times
7. On average, how many visitors did you have to your home in a week, excluding an intimate partner?
    a. 0-2
    b. 2-4
    c. 4-6
    d. >6

Sleep, Mood and Quality of Life

1. How many hours of sleep are you getting each night?
    a. 2-6 hours
    b. 6-8 hours
    c. 8-10 hours
    d. >10 hours
2. How often have you felt sad/low for no good reason?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
3. How often have you felt anxious or panicky for no good reason?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
4. How often have you looked forward with enjoyment to things?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
5. How often have you felt like you were having trouble coping with things?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
6. How often have you felt that you have someone with whom you can share your joys, sorrows and anxieties with?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
7. How often have you felt that you have someone to count on when you need help?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
8. How often have you felt unable to cope with performing your usually day to day activities alongside your pregnancy?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
9. How satisfied do you feel with your social life right now?
    a. No satisfaction
    b. Some satisfaction
    c. Mostly satisfaction

d. Complete satisfaction

Study Experience (For intervention group only, included as part of the final survey)

1. How difficult do you feel it was to comply with the lockdown measures in this study?
    a. Very difficult
    b. Mostly difficult
    c. Neither difficult nor easy
    d. Mostly easy
    e. Very easy
2. Which measure was the most difficult to comply with?
    a. Maintaining 1.5m distance between yourself and another individual
    b. Wearing a face covering
    c. Performing hand hygiene prior to touching your nose/mouth
    d. Remaining withing 5km of your residence
    e. Remaining at home between 9pm-5am, except for essential purposes (work/study or to seek/give care)
    f. Only leaving home for essential purposes (work or study, to seek/give care or for outside exercise)
    g. Refraining from having visitors to your home except for an intimate partner
3. How disruptive were these lockdown measures to your day-to-day life?
    a. Very disruptive
    b. Mostly disruptive
    c. Somewhat disruptive
    d. Not disruptive at all
4. If we could definitively prove that lockdown decreased the risk of preterm birth, do you feel that this is a reasonable set of measures to ask pregnant women to comply with?
    a. Yes
    b. No
5. Do you feel that the lockdown measures you were required to comply with put a strain on your partner/friends/family?
    a. Yes (specify why/how)
    b. No
6. Was the wrist device you were asked to wear comfortable?
    a. Yes
    b. No
7. Did you feel it was reasonable to ask pregnant women to wear the wrist device for the duration of their time in the trial?
    a. Yes
    b. No
8. Were there any reasons why you felt you could not wear the device or had to remove it for extended periods of time (e.g more than 3 hours)?
    a. Yes (please specify when/why)
    b. No
9. Please feel free to add any other thoughts/comments/concerns about your experience in this study:
    a. ……..

iPREM Pilot Trial: Reporting Checklist

		Reporting Item	Page Number
Administrative information			
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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 15
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2

Roles and responsibilities: sponsor and funder	#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 – sponsor/funders did not play any roles in study design
Roles and responsibilities: committees	#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)	12, 13
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	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5, 6
Objectives	#7	Specific objectives or hypotheses	6

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, non-inferiority, exploratory)	6
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	7
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)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in	N/A - the intervention will not be modified for any given trial participant.

		response to harms, participant request, or improving / worsening disease)	
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A - as this is a feasability trial, there is no specific adherence recommendations given this is what we are measuring in the first instance.
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	9-11
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 (see Figure)	8, 9

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	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
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	7
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	7

Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A - participants and healthcare staff are not blinded. There are no circumstances under which emergency unblinding of data collectors/analysts will be required.
Methods: Data collection, management, and analysis			
Data collection plan	#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,	10, 11

		laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	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	12
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	13, 14
Statistics: outcomes	#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	11, 12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11, 12

Statistics: analysis population and missing data	#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)	11, 12
Methods:			
Monitoring			
Data monitoring: formal committee	#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	12, 13
Data monitoring: interim analysis	#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	13
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	12

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
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)	11
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
Consent or assent: ancillary studies	#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	13, 14

		confidentiality before, during, and after the trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13, 14
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	13
Dissemination policy: trial results	#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	13, 14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	14
Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A

reproducible research			

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	See supplementary material
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

Notes:

- 5c: N/A - sponsor/funders did not play any roles in study design
- 11b: N/A - the intervention will not be modified for any given trial participant.
- 11c: N/A - as this is a feasability trial, there is no specific adherence recommendations given this is what we are measuring in the first instance.
- 17b: N/A - participants and healthcare staff are not blinded. There are no circumstances under which emergency unblinding of data collectors/analysts will be required. The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 24. April 2023 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Feasibility of a pregnancy intervention mimicking viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women enrolled in antenatal clinics in Melbourne, Australia: protocol for a pilot, randomised trial

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Complete List of Authors:	Sridhar, Shivadharshini; Monash Medical Centre Clayton, Department of Obstetrics and Gynaecology ; Monash University, Department of Obstetrics and Gynaecology Mol, Ben; Monash University, Department of Obstetrics and Gynaecology ; Monash Medical Centre Clayton, Department of Obstetrics and Gynaecology Hodges, Ryan; Monash Medical Centre Clayton, Department of Obstetrics and Gynaecology; Monash University, Department of Obstetrics and Gynaecology Palmer, Kirsten; Monash University School of Clinical Sciences at Monash Health, Obstetrics and Gynaecology ; Monash Medical Centre Clayton, Department of Obstetrics and Gynaecology Sundram, Suresh; Monash University, Department of Psychiatry; Monash Medical Centre Clayton, Mental Health Program de Carvalho Pacagnella, Rodolfo; University of Campinas Institute of Biology, Department of Obstetrics and Gynaecology Souza, Renato; University of Campinas Institute of Biology, Obstetrics and Gynecology Barbosa-Junior, Francisco; University of Sao Paulo, Department of Social Medicine Mackin, David; Sunshine Hospital, Department of Maternal Fetal Medicine Said, Joanne; The University of Melbourne; Sunshine Hospital, Department of Maternal Fetal Medicine Rolnik, Daniel ; Monash University; Monash Medical Centre Clayton, Department of Obstetrics and Gynaecology Malhotra, Atul; Monash University, Department of Paediatrics; Monash Children's Hospital
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Paediatrics, Infectious diseases
Keywords:	COVID-19, NEONATOLOGY, OBSTETRICS

PROTOCOL PAPER

Long Title: Feasibility of a pregnancy intervention mimicking viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women enrolled in antenatal clinics in Melbourne, Australia: protocol for a pilot, randomised trial

Short Title: iPREM Pilot (Isolate to Prevent pretERM birth)

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ABSTRACT

Introduction: Preterm birth is a leading cause of perinatal morbidity and mortality. During the COVID-19 pandemic, reduction in rates of preterm birth in women exposed to viral mitigation measures was reported by multiple studies. In addition, others and we observed a more pronounced reduction of preterm birth in women who had previously experienced a preterm birth. The aim of this pilot study is to establish the feasibility of a lifestyle intervention based on viral mitigation measures in high-risk pregnancies, with the ultimate aim to reduce the incidence of preterm birth.

Methods and Analysis: One hundred pregnant women, enrolled in antenatal clinics at two tertiary maternity centres in Melbourne, Australia, who have had a previous preterm birth between 22-34 weeks gestation will be recruited. This is a two-arm, parallel group, open-label randomised controlled feasibility trial: fifty women will be randomised to the intervention group, where they will be requested to comply with a set of lifestyle changes (similar to the viral mitigation measures observed during the pandemic). Another fifty women will be randomised to the control group, where they will undergo standard pregnancy care. The primary outcome of this trial is feasibility, which will be assessed by measuring patient eligibility rate, recruitment rate, compliance rate and data completion rate. Secondary outcomes include incidence of preterm birth, maternal satisfaction, maternal quality of life and other pregnancy outcomes. Standard methods in statistical analysis for randomised controlled trials on an intention to treat basis will be followed.

Ethics and Dissemination: This trial has been approved by the Monash Human Research Ethics Committee; approval reference number RES-22-0000-122A. Study findings will be reported and submitted to peer-reviewed journals for publication, and presentation at conferences.

Trial Registration Number:

ACTRN12622000753752; pre-results

ARTICLE SUMMARY

Strengths and Limitations of the Study

- This study is a randomised controlled trial investigating the feasibility of a pregnancy intervention that mimics viral mitigation measures on preterm birth rates.
- Outcomes are measured using both subjective (surveys) and objective (actigraphy device data) measures to provide a comprehensive range of data regarding acceptability of the intervention.
- Compliance to the intervention is self-reported.
- Due to the nature of the intervention, it is not possible to blind patients or clinicians involved in the recruitment process.

INTRODUCTION

Preterm birth, defined as delivery prior to 37 weeks gestation, is the leading cause of perinatal morbidity and mortality worldwide. Globally, approximately 15 million preterm births occur yearly and more than 1 million babies die shortly after birth as a direct result of their prematurity.(1) In Australia, 8.6% of deliveries are preterm with the average gestational age at birth being 33 weeks.(2) Preterm delivery occurs after the following obstetric precursors: spontaneous preterm labour (40-45%), preterm premature rupture of membranes (PPROM, 25-30%) or where delivery is indicated due to maternal or fetal compromise (30-35%).(3) An increasing degree of prematurity is known to correlate with a greater risk of complications including neurodevelopmental delay, cerebral palsy and cardio-respiratory disease.(4) Prematurity also has a significant economic impact; 72% of preterm infants will need admission to the neonatal intensive care unit where the average length of admission is 28 days and the cost per day is almost $2000.(2, 5) Mothers of preterm infants take longer to return to work, have a lower medium income and increased out of pocket healthcare costs. (6)

The exact causality of preterm birth remains unknown, however risk factors include previous preterm birth, maternal age, smoking, multiple gestation, gestational diabetes, maternal literacy level and social disadvantage.(3) Although we have methods to manage high risk women including progesterone treatments, aspirin and cervical cerclage, overall preterm birth rates have continued to rise in most industrialised nations. (7, 8)

The outbreak of COVID-19 brought the world to a standstill, having drastic social and economic impacts. The first Australian case was detected in Victoria in January 2020 and by March, measures including social distancing, wearing face masks and performing hand hygiene were introduced to mitigate virus spread.(9) Unexpectedly, it has been observed around the world that pregnant women exposed to mitigation measures for the COVID-19 virus have had a reduction in preterm birth rates by 20-30%, with this effect being more pronounced in early preterm birth (<34 weeks).(10-12) At Monash Health in Melbourne, an observational study demonstrated a 30% reduction in preterm birth rate prior to 34 weeks (risk ratio (RR) 0.74 (95% CI, 0.57-0.96; p = 0.021). This effect was stronger in women who had experienced a previous preterm birth (RR 0.42, 95% CI 0.21-0.82; p = 0.008) when compared to parous women who had not experienced a preterm birth (RR 0.93, 95% CI 0.63-1.28; p = 0.714).(13)

We hypothesise that in women with a previous preterm birth (<34 weeks), a pregnancy intervention mimicking COVID-19 mitigation measures will reduce the incidence of a subsequent preterm birth. We propose that the mechanism of action behind this effect may be due to a reduction in physical activity, stress, noise or air pollution, medical interventions and/or reduced rates of infection.

While observational studies, including those conducted by our team, have demonstrated that COVID-19 mitigation measures have an effect on preterm birth rates, these findings are inconsistent, it is unclear which aspect of these measures contribute to the phenomenon, and there have been no randomised controlled trials that have further investigated this effect to establish causality. We believe that we have a unique opportunity to study this effect further as we are based in Melbourne, where the population has been subject to some of the harshest lockdowns. However, we must first assess feasibility of such an intervention in pregnancy prior to conducting any larger randomised trials.

AIM

The aim of this study is to investigate the feasibility of a lifestyle intervention in pregnancy that mimics viral mitigation measures in pregnant women who have previously had a preterm birth between 22-34 weeks.

METHODS AND ANALYSIS

Study Design

This is a multi-site, two-arm open-label randomised controlled clinical trial that will be conducted across tertiary maternity centres in Melbourne, Australia. The Standard Protocol Items: Recommendations for Interventional Trials checklist was used to prepare this report.(14) The flowchart of the study design is shown in Figure 1. The flowchart of the study design is shown in Figure 1. This trial was registered with the Australia New Zealand Clinical Trials Registry on 26th May 2022 (Table 1).

Data Category	Information
Primary registry and trial identifying number	Australian New Zealand Clinical Trials Registry ACTRN12622000753752
Date registered	26 May, 2022
Source(s) of monetary or material support	Monash Health Monash University
Primary Sponsor	Monash Health
Secondary Sponsor	Monash University
Contact for Public and Scientific Queries	Associate Professor Daniel Rolnik Email: daniel.rolnik@monash.edu
Public Title	iPREM Pilot (Isolate to Prevent pretERM birth)
Scientific Title	Feasibility of a pregnancy intervention mimicking viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women enrolled in antenatal clinics in Melbourne, Australia: protocol for a pilot, feasibility randomised trial
Countries of Recruitment	Australia
Health condition(s) studied	Premature birth
Intervention(s)	Active comparator: Pregnancy intervention mimicking COVID-19 viral mitigation measures
	Control comparator: Standard pregnancy care
Key inclusion and exclusion criteria	Inclusion: Pregnant women ≥18 years, previous preterm birth between 22-34 weeks gestation
	Exclusion criteria: Fetus with major congenital abnormality
Study Type	Interventional
	Allocation: randomized interventional model
	Primary purpose: feasibility
Date of first enrolment	July 2022
Target sample size	100
Recruitment status	Recruiting
Primary Outcome (s)	Feasibility

Secondary Outcome(s)	Preterm birth < 34 weeks, maternal quality of life and satisfaction and other pregnancy outcomes

Table 1: Trial Registration Data

Sample Size

Given the primary objective of this trial is to establish feasibility, we aim to recruit up to one hundred pregnant women, fifty of whom will be randomised to the intervention group and fifty of whom will be randomised to the control group. We chose this sample size as we estimated that at our initial recruitment site, there may approximately 150-200 eligible women and so a sample size of one hundred (i.e. half of the eligible population) would be representative of the overall group.

Patient Population

Adult pregnant women receiving care at antenatal clinics who are at 'high risk' for having a preterm birth, where 'high risk' will be defined as having had a previous preterm birth between 22-34 weeks gestation.

Inclusion Criteria

Pregnant women, singleton or multiple gestation, will be eligible for this trial if they are aged 18 years or over and have previously delivered a preterm baby between 22+0 and 34+0 gestation, either spontaneously or iatrogenically. Women must primarily speak English and have the ability to read and write.

Exclusion Criteria

Pregnant women will be excluded if they are carrying a fetus with one or more major congenital abnormalities.

Recruitment

Pregnant women who are enrolled in each recruitment site's antenatal clinics will be screened by a clinical team who are familiar with the eligibility criteria. We will make an entry onto the relevant medical records system flagging eligible women. We will also brief clinicians in the clinic on the study details so that they can refer any eligible patients we may have missed in our initial screening process. Additionally, we will display flyers advertising the study in clinic rooms so women who feel they are eligible can contact the

research team themselves. When an eligible woman presents to the clinic, we will ask her treating clinician to briefly explain the study and provide her with a patient invitation form. A member of our research team will then approach eligible patients and explain trial details prior to recruitment. Prospective participants will be given 48 hours to consider whether they would like to take part in the trial. If the patient agrees to participate in the trial, they will be asked to sign a written consent form. We will ensure to obtain and store an individual record of all non-recruited patients, including their reasons for exclusion.

No members of the research team will be involved in the care of potential participants at the site of recruitment, ensuring that there are no unequal or dependent relationships. This study will not be blinded to participants as well as nurses, midwives, doctors, or investigators who are involved in the recruitment process. The investigator collecting study outcome data once a participant has completed the trial and the investigator who analyses the data will be blinded to the group to which participants were allocated.

Recruitment commenced in June 2022 and is expected to take around 18-24 months for completion.

Randomisation

Pregnant women who are successfully recruited are randomised and allocated on the first day of the trial using Research Electronic Data Capture (REDCap, Version 12.4.10, Vanderbilt University) by a member of the research team. REDCap is a secure, web-based data collection and management software that meets Health Insurance Portability and Accountability Act (HIPAA) compliance standards.(15, 16) The randomisation table was generated by using the statistical software Stata, with variable block sizes of 2 and 4.(17)

Interventions

Intervention Group

This pregnancy intervention is designed to mimic the stage 3 and 4 COVID-19 virus mitigation measures implemented in metropolitan Melbourne, Australia in 2020-21. Briefly, this involved social distancing, restrictions to movements outside the home unless necessary, imposition of a curfew as well as hygiene recommendations including hand hygiene and mask wearing.(9) Originally, alongside their standard pregnancy care, study

participants were asked to comply with the following measures for the duration of the intervention.

1. Refrain from leaving their homes unless required to do so, such as shopping for essentials, to work or study, to seek or give care, for safety purposes (e.g. escaping domestic violence) or for outside exercise.
2. Avoid having visitors to their home unless it is their intimate partner and try to maintain social distancing where possible, that is, a 1.5m distance between themselves and another party unless in their own home or with an intimate partner.
3. Wear a face mask or covering when outside their home and perform hand hygiene prior to removing their mask or touching any aspect of their nose or mouth.
4. Aim to remain at home between 9 pm and 5 am unless they are required to leave for work or study or to seek or give care and avoid travelling beyond 5km of their place of residence except for essential reasons.

Initial recruitment rates were approximately 30%, i.e 30% of eligible participants consented to take part in the trial and the majority of eligible participants who declined to take part did so as they felt that the intervention was too strict. In order to increase recruitment, the research team made the decision to relax the requirements of the intervention. As of now, participants who are assigned to the intervention group will be asked to comply with the following:

1. Try to minimise the number of visitors to their home and refrain from attending large social gatherings where possible.
2. Remain in their homes unless required to do so, such as for study/work, shopping for essentials, to seek/give care, for outdoor exercise or if their home environment becomes unsafe in any way (e.g domestic violence).
3. Wear a face mask/covering when outside their home and perform hand hygiene prior to removing their mask/touching any aspect of their nose or mouth.

Standard pregnancy care will be defined as routine antenatal care appointments, ultrasound scans, pathology and any other investigations or treatments required as determined by the participant's antenatal care team.

Control Group

Participants randomised to the control group will undergo standard pregnancy care without any restrictions.

Participants will begin the trial intervention two weeks prior to the gestational age at which the study participant's previous preterm birth occurred (i.e., if they delivered in their previous pregnancy at 32^{+3} weeks, their first day in the trial will be at 30^{+3} weeks). If the participant has had multiple preterm births, they will begin the trial 2 weeks prior to the gestational age of their earliest preterm delivery. The maximum gestation for recruitment will be 31 weeks to ensure that the participant is in the trial for at least 3 weeks. Therefore, if they previously gave birth at 33^{+6} weeks gestation, they will be required to begin the study at 31 weeks gestation. The duration of the intervention will be six weeks (i.e., two weeks prior and four weeks post the gestational age of the previous preterm birth) or until 34 weeks gestation or until birth, whichever comes first.

All participants will be required to complete short, online surveys (which will be developed and distributed to their email via REDCap) to assess their hygiene, social contacts, activities, mood and quality of life at baseline and then on a fortnightly basis for the duration of their time in the trial (see supplementary material).

All participants will also be encouraged to wear an actigraphy device (provided by the study team), similar to a watch, on their non-dominant wrist, 24 hours a day, for the duration of their time in the trial. For the purposes of this study, we have chosen the GENEActiv Original (Activinsights, Kimbolton, United Kingdom). It is a 43x40x13mm water resistant device, which has an inbuilt tri-axial piezoelectric accelerometer, light intensity and temperature sensors. The device will be set to record data at a sampling rate frequency of 20Hz. As sampling rate has a direct impact on the actigraph's battery life, this will enable the participant to wear the device for four weeks without requiring a re-charge. We will configure the device to automatically start recording on the participant's first day in the trial so they will not be required to push any buttons. If the participant remains in the trial for greater than four weeks, a research assistant will collect the old device from them and provide them with a new, charged device. Once the participant has finished their time in the trial, raw data will be downloaded from the devices using the GENEActiv PC Software (Version 3.3, Activinsights) as a '.bin' file and analysed.

Patient and Public Involvement

The study team consulted patients and clinicians at the antenatal clinic where recruitment is taking place for their advice and input into the design of the study.

OUTCOMES

Primary Outcome

Feasibility

We will measure feasibility using the following criteria:

Patient eligibility rate, which will be measured as the proportion of eligible women screened at the antenatal clinic who are expected to consent to taking part in this trial. We have set a pre-defined target of 50%.

Patient recruitment rate, which will be measured as the proportion of eligible women that consent to taking part in the study who are randomised (noting that there may be a significant time period between consent and randomisation). We have set a pre-defined target of 50%.

Compliance rate, which will be measured as the proportion of participants in the intervention group who are considered to have good compliance with the intervention. This will be measured via fortnightly, participant filled surveys and we will set a pre-defined target of 75%. On each fortnightly survey, participants will be asked questions pertaining to their compliance with each restriction measure. For example, participants will be asked how often they wore a mask when outside their home and if they were to answer either 'most of the time' or 'all of the time', we would classify this as having $\geq$ 75% compliance with this restriction measure. Participants must report $\geq$ 75% compliance for all restriction measures in order to be defined has having 'good compliance' with the intervention. This will be measured at the end of the trial.

Data completion rate, which will be measured as the proportion of trial participants who complete the final survey (i.e., the survey that the participant is required to complete once they reach an endpoint). This will be measured at the end of the trial. We have set a pre-defined target of $\geq$ 75%.

Secondary Outcomes

Secondary outcomes will include incidence of preterm birth prior to 34 weeks gestation, maternal satisfaction, and quality of life as well as other pregnancy outcomes such as pregnancy duration, incidence of stillbirth and incidence of iatrogenic or spontaneous delivery. We will measure maternal satisfaction and quality of life via fortnightly surveys we have developed based on previously validated questionnaires including but not limited to the Beck Depression Inventory, QOL-GRAV and Multidimensional Scale of Perceived Social Support. We will also collect non-dominant wrist raw acceleration data through the actigraphy device. The raw acceleration data will be used to derive physical activity patterns, estimate sleep-wake cycle and verify the compliance with wearing the device.

Other data to be collected

Demographic data collected will include maternal demographic data such as birth country, age, marital status, medical history, drug use, risk factors for preterm birth, gravida/parity, obstetric history, details of current pregnancy, incidence of prelabour premature rupture of membranes, incidence of presumed chorioamnionitis, use of antenatal steroids, mode of delivery and maternal death. We will also collect infant demographic data such as birthweight in grams.

Other neonatal outcomes collected will include incidence of admission to neonatal intensive care (NICU) or special care nursery (SCN), incidence of NICU stay >48 hours, neonatal morbidity (5-minute Apgar score <5, respiratory distress syndrome requiring intubation, grade 3 or 4 intraventricular haemorrhage, neonatal seizures, culture-positive neonatal sepsis, retinopathy of prematurity requiring treatment, necrotising enterocolitis) and neonatal death.

A member of the research team will download data from the actigraphy device from the device after the participant has completed their time in the trial. Once the participant has given birth, secondary and other data will be collected by a member of the research team who is blinded to participant's allocation.

DATA ANALYSIS

We will use the open-source package GENEActiv and GENEA In R (GGIR, Version 2.5) to translate raw actigraphy data to readable information.(18) Data will be downloaded from

each device as a .bin file, which will be read and translated to a .csv file by the GGIR package according to predefined parameters. Initially, GGIR will perform sensor calibration in the data collected to check and correct calibration errors in the accelerometer(19). Due to the raw data size, we will set GGIR to summarise the collected 20 Hz sample-rate data to 5s epochs.

Feasibility targets will be assessed first. Baseline continuous covariates will be expressed as mean and standard deviation or median and interquartile range depending on the distribution of the data as assessed by inspection of histograms and quantile-quantile (QQ) plots. Normally distributed continuous variables will be compared between the groups using independent-samples t-test, and non-normally distributed variables will be compared between the trial arms with the Wilcoxon rank-sum test.

Categorical variables will be expressed as counts and percentages and compared between the study groups using the Chi-squared test or Fisher's exact test, as appropriate. Descriptive statistics will be reported for assessment of feasibility as previously defined in the study outcomes section.

The effect of the intervention on the odds of preterm birth and other binary pregnancy outcomes will be modelled using univariable logistic regression models and expressed as the odds ratio with 95% confidence intervals. Multivariable models will be used to adjust for covariates with significant imbalances between the groups at baseline, if needed. Analyses will be performed according to an intention-to-treat principle, and secondary per protocol analysis will be performed including only participants from the intervention group with compliance ≥ 75%.

All statistical analyses will be conducted in the statistical environment R, and p-values below 0.05 will be considered statistically significant. We will report findings in accordance with Consolidated Standards of Reporting Trials guidelines.

ADVERSE EVENTS

Serious Adverse Events (SAE)

SAEs will be defined as any event required admission to hospital (excluding admission for delivery), maternal or fetal death, fetal malformations, any event that leads to maternal

disability and any event where a participant contacts the study team with concerns regarding a serious deterioration in their mental health during the trial.

Adverse Events (AE)

Any other event reported by a participant or their partner not needing hospital admission or not falling in a category of SAEs.

DATA SAFETY MONITORING BOARD (DSMB)

An independent DSMB comprising of a senior research fellow in obstetrics and gynaecology, a consultant neonatologist and a perinatal epidemiologist has been formed to review the study, the data generated and ensure safety of all participants. Members of the DSMB do not have a vested financial, scientific, or other conflict of interest with this trial. All SAEs will be reported to the data safety monitoring board (DSMB) within 24-48 hours of the team becoming aware of the event.

An interim analysis evaluating the safety of the trial will be conducted after fifty eligible women have been screened. The DSMB will be required to evaluate any adverse events and assess the ongoing safety of the trial. They will have the ability to suspend or terminate the study if required on the basis of a lack of feasibility or any SAEs observed. Given the feasibility nature of the trial and that the interim analysis will only assess safety, no sequential trial adjustments to the alpha level will be made.

REPORTS TO HUMAN RESEARCH ETHICS COMMITTEE (HREC)

Any SAEs that the DSMB deem will necessitate a temporary halt of the trial pending review and any changes to the protocol or patient information consent form (PICF) will be reported to the HREC. We will also ensure to provide an interim report following the recruitment of fifty participants to the trial as well as an annual research progress report.

ETHICS AND DISSEMINATION

Ethics

This study has been approved by the Monash Health Human Research Ethics Committee and will be conducted in accordance with the approved protocol/amendment(s) and NHMRC National Statement on Ethical Conduct in Human Research 2007 (updated 2018). The study will also comply with the Declaration of Helsinki and with the Good Clinical Practice (GCP) standards. An expert team of senior obstetricians, neonatologists,

researchers and psychiatrists were consulted regarding the intervention and protecting the psychological safety of the women in the trial. We have ensured that participants have ample opportunity to contact the study team if they are concerned and have developed the surveys in consultation with a psychiatrist to appropriately assess the quality of life of trial participants.

Data for this trial will be collected from electronical medical records system, surveys completed by participants and from actigraphs utilised by participants following informed consent. Each participant will be assigned a unique participant identifier which will be the only number that appears on their reports to maintain confidentiality. Only authorised members of the research team will be able to log into the secure web-based portal, REDCap, to input trial data for each participant using their unique participant identifier. De-identified actigraph device data will be stored in a password protected computer file, also only accessible to authorized members of the research team. All data will be stored for 15 years after which it will be disposed of via permanent deletion.

Consent

Informed, written consent will be obtained using a specifically designed PICF (see supplementary material) from potential participants after a member of the research team has ensured that the participant understands the study procedures involved, the potential benefits and/or risks as well as the expected duration of the intervention. Participants will be made aware that their participation is entirely voluntary and that they are free to withdraw at any stage for any reason. The research team member will also inform participants that withdrawal of consent will not affect their relationship with their physician or their right to appropriate medical treatment.

Dissemination

The study results will be disseminated by publication in peer-reviewed journals and presented at conferences as appropriate.

OTHER

Author Contributions: The initial concept was developed by AM, DLR and BWM. All authors contributed to the design of the study. Shivadharshini S drafted the ethics application, protocol, case report forms, surveys and manuscript. AM, DLR, BWM, RH, KRP, Sundram S, RCP, RTS, FB-J, DM and JS made critical revisions and assisted with ethics application submission, editing of protocol and editing of manuscript. All authors have read and approved the final manuscript and are accountable for its accuracy.

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Competing Interests: None declared

Patient Consent for Publication: Not required

Provenance and Peer Review: Not commissioned; externally peer reviewed.

REFERENCES

1. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller A-B, et al. Born Too Soon: The global epidemiology of 15 million preterm births. Reproductive Health. 2013;10(1):S2.
2. Welfare AIoHa. Australia's Mothers and Babies 2016 - in brief. Perinatal Statistics Series. Canberra: Australian Institute of Health and Welfare; 2018.
3. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. The Lancet. 2008;371(9606):75-84.
4. Organization WH. Born Too Soon. The Global Action Report on Preterm Birth. Geneva: World Health Organization; 2012.
5. Zainal H, Dahlui M, Soelar SA, Su TT. Cost of preterm birth during initial hospitalization: A care provider's perspective. PloS one. 2019;14(6):e0211997-e.
6. Fox H, Callander E. Cost of preterm birth to Australian mothers: Assessing the financial impact of a birth outcome with an increasing prevalence. Journal of Paediatrics and Child Health. 2021;57(5):618-25.
7. Chawanpaiboon S, Vogel JP, Moller A-B, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. The Lancet Global Health. 2019;7(1):e37-e46.
8. Newnham JP, Dickinson JE, Hart RJ, Pennell CE, Arrese CA, Keelan JA. Strategies to prevent preterm birth. Frontiers in immunology. 2014;5:584-.
9. Storen RC, N. COVID-19: a chronology of state and territory government announcements (up until 30 June 2020). In: Services P, editor. Canberra: Parliamentary Library 2020.
10. Philip RK, Purtill H, Reidy E, Daly M, Imcha M, McGrath D, et al. Unprecedented reduction in births of very low birthweight (VLBW) and extremely low birthweight (ELBW) infants during the COVID-19 lockdown in Ireland: a 'natural experiment' allowing analysis of data from the prior two decades. BMJ Global Health. 2020;5(9):e003075.
11. Been JV, Burgos Ochoa L, Bertens LCM, Schoenmakers S, Steegers EAP, Reiss IKM. Impact of COVID-19 mitigation measures on the incidence of preterm birth: a national quasi-experimental study. The Lancet Public Health. 2020;5(11):e604-e11.
12. Matheson A, McGannon CJ, Malhotra A, Palmer KR, Stewart AE, Wallace EM, et al. Prematurity Rates During the Coronavirus Disease 2019 (COVID-19) Pandemic Lockdown in Melbourne, Australia. Obstetrics & Gynecology. 2021;137(3).
13. Rolnik DL, Matheson A, Liu Y, Chu S, McGannon C, Mulcahy B, et al. Impact of COVID-19 pandemic restrictions on pregnancy duration and outcome in Melbourne, Australia. Ultrasound in Obstetrics & Gynecology. 2021;58(5):677-87.
14. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Annals of internal medicine. 2013;158(3):200-7.
15. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.
16. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
17. StataCorp. Stata Statistical Software: Release 17. 17 ed. College Station, TX: StataCorp LLC; 2021.
18. Migueles JH, Rowlands AV, Huber F, Sabia S, van Hees VT. GGIR: A Research Community–Driven Open Source R Package for Generating Physical Activity and Sleep

Outcomes From Multi-Day Raw Accelerometer Data. Journal for the Measurement of Physical Behaviour. 2019;2(3):188-96.
19. Hees VTv, Fang Z, Langford J, Assah F, Mohammad A, Silva ICMd, et al. Autocalibration of accelerometer data for free-living physical activity assessment using local gravity and temperature: an evaluation on four continents. Journal of Applied Physiology. 2014;117(7):738-44.

FIGURE LEGEND

Figure 1 – Flow Chart.

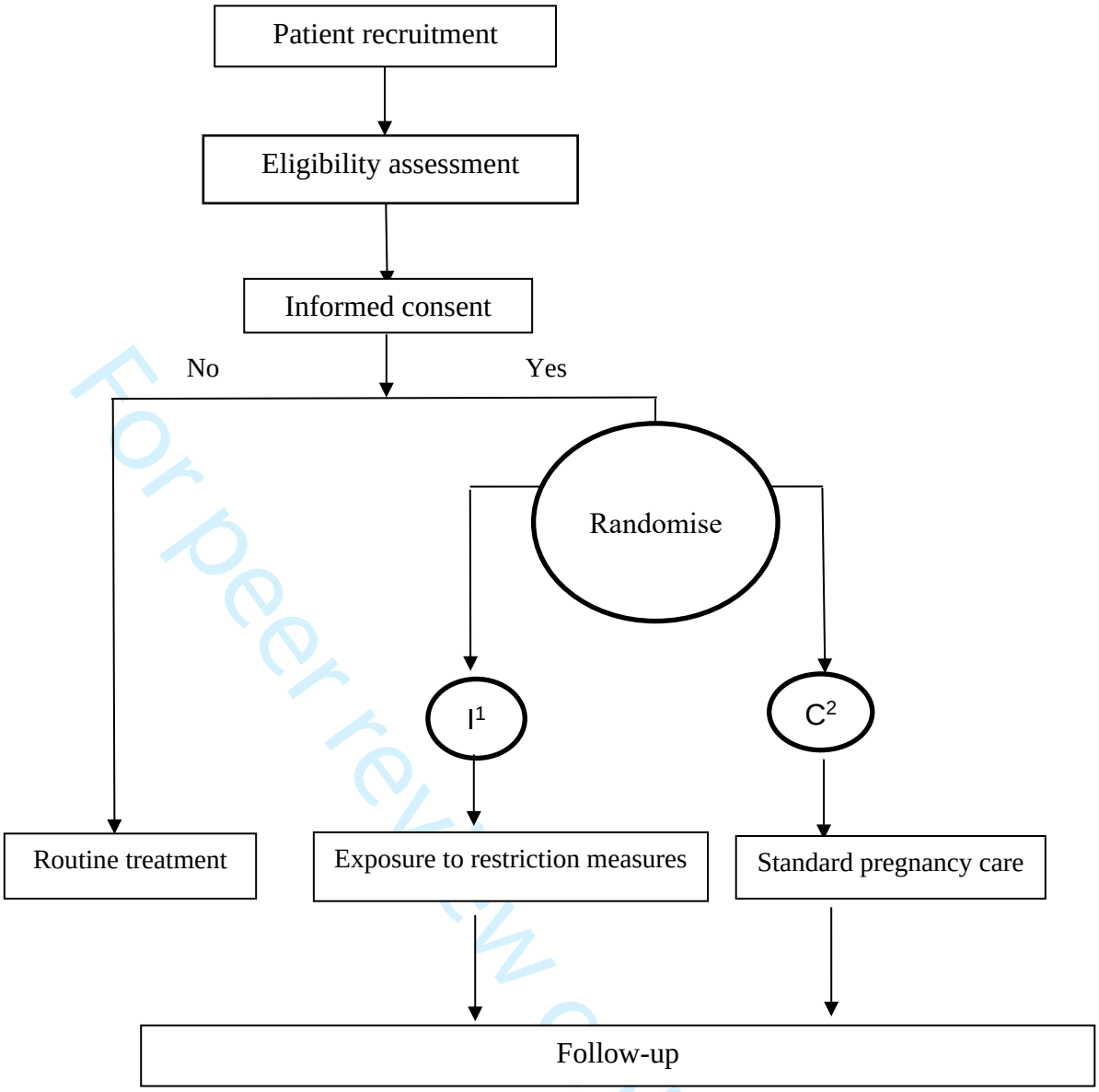

Figure 1. Flowchart.

1 Intervention

2 Control

Effect of viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women: protocol for a pilot, feasibility randomised trial

Shivadharshini Sridhar[1,2], Ben W Mol[1,2], Ryan Hodges[1,2], Kirsten R Palmer[1,2], Suresh Sundram[3,4], Rodolfo Carvalho Pacagnella[5], Renato T Souza[5], Francisco Barbosa-Junior[6], David Mackin[7], Joanne Said[7,8], *Daniel L Rolnik[1,2], *Atul Malhotra[9,10,11]

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SUPPLEMENTARY MATERIAL

PARTICIPANT INFORMATION AND CONSENT FORM (MASTER)

Title	Randomised controlled trial investigating the effect of viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women
Short Title	iPREM (Pilot)
Project Sponsor	Monash Health
Principal Investigator(s)	Professor Ben Mol
Associate Investigator(s)	Dr A/Prof Daniel Rolnik A/Prof Atul Malhotra Dr Shivadharshini Sridhar

Part 1 What does the participation involve?

1 Introduction

We are inviting you to take part in this research project because you are currently pregnant and have previously given birth to a preterm baby (i.e. a baby born between 22 and 34 weeks of gestation). Your information was obtained from our medical records system.This research project is investigating the feasibility and safety of an intervention in pregnancy that may decrease the risk of preterm birth.

This participant information and consent form will explain the purpose of our project and what it will involve as clearly as possible so that you can be fully informed before you decide whether you would like to take part.

Please take your time to read through this statement carefully. If you have any questions or concerns, please do not hesitate to contact our researcher via email or phone. Before deciding whether you would like to participate, you may want to talk about it with a family member or a medical professional.

Participation in this research project is voluntary and if you decide you do not wish to take part, you do not have to. You will still receive the best possible care regardless of whether you are involved with our study.

If you do decide to take part, you will need to sign the consent section. By signing this, you are telling us that:

- You understand everything you have read in this statement
- You consent to your participation in this project
- You consent to the use of your personal and health information as described

You will be given a copy of this participant information and consent form to keep.

2 What is the purpose of this research?

Preterm birth (i.e. when a baby is born too early) occurs in around 9% of all deliveries in Australia and can be associated with significant medical consequences for babies. During the COVID-19 pandemic, we, and many other groups around the world have observed that women who have been pregnant during lockdown have experienced a decreased rate of preterm birth. At Monash Health, a 30% decrease in women giving birth before 34 weeks of gestation was observed and this effect was stronger in women who had a previous preterm birth. We believe that this phenomenon may have to do with changes in the way we lived during lockdowns - physical distancing, changes in physical activity, work from home and possibly improved hygiene.

The purpose of this study is to investigate whether it is feasible to conduct an intervention in pregnancy that mimics the COVID-19 lockdowns and observe if there is an associated decrease in the rate of preterm birth in women who have previously experienced a preterm birth. Once we can establish feasibility and safety of this intervention, larger studies may be conducted to further establish whether these measures actually decrease preterm birth rates.

This research has been initiated by a research team led by Professor Ben Mol. This team, alongside the associate investigators listed above have experience looking after pregnant women and premature babies.

3 Who is organising and funding the research?

This research project is being conducted and led by Professor Ben Mol and his research team.

4 What does participation in this research involve?

If we determine that you are eligible to participate and you choose to take part in this study, you will be required to sign the consent form below.

We are inviting 100 women to take part in this study. 50 women will be randomly assigned to the 'control' group and undergo standard pregnancy care with no changes. 50 women will be randomised to the 'intervention' group, where they will be asked to comply with a pregnancy intervention that mimics the lockdown measures implemented in Melbourne to prevent the transmission of COVID-19.

If you are part of the pregnancy intervention group, you will be asked to try and comply with the following measures to the best of your ability for the duration of the study:

- Refrain from attending social gatherings and maintain 1.5m distance between yourself and another individual when outside your home
- Try to wear a face mask or covering whenever you leave your home
- Try to perform hand hygiene prior to touching your nose or mouth
- Try to remain in your home unless you must leave for study/work, for essential services, to seek**,** safety purposes (e.g you do not feel safe in your home) or give care or to do outdoor exercise
- Try to remain at home between the hours of 9pm-5am unless you must leave for work/study**,** safety purposes or to seek/give care
- Avoid having visitors to your home unless they are an intimate partner
- Try not to travel beyond 5km from your place of residence

We understand that there may be certain circumstances that mean you cannot follow through with all the above recommendations, for example, important events that you must attend such as a wedding or funeral. You are of course free to attend at your discretion, we just ask that wherever you can, please try to follow the recommendations as much as possible. For instance, if you attend a wedding, consider following at least some of the recommendations such as wearing a facemask and performing hand hygiene.

The study will begin 2 weeks before the gestation at which you gave birth to your previous preterm baby (i.e. if you gave birth at 32 weeks, the study would begin at 30 weeks gestation of your current pregnancy). However, if your previous preterm baby was born at 33+6 weeks gestation, the study will begin at 30+6 weeks gestation of this pregnancy so that you are in the study for at least 3 weeks. It will be conducted for 6 weeks (i.e. 2 weeks before and 4 weeks after the gestational age of your previous preterm birth), until 34 weeks gestation or until birth – whichever comes first.

You will be asked to complete a 5-10 minute fortnightly surveys over the course of the study about your work, household contacts, physical activity, hygiene practices, mood and quality of life. You will also be asked to wear a device on your wrist (figure 1), similar to a watch, that will record physical activity, temperature, light and sleep for the duration of your time in the study.

Figure 1. Actigraphy device.

You will not be paid to take part in this research project and there will be no additional costs to you associated with your participation.

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

Participation in this trial is entirely voluntary and if you do not wish to take part you are in no way obligated to. If you decide to take part and then change your mind, you are free to withdraw at any stage – you can easily do this by contacting the researcher via email or phone and informing them of your wish to withdraw.

If you do decide to take part, you will be given a copy of this patient information consent form to sign and a copy to keep.

Your decision to take part, or not take part in this study will not affect your relationship with your doctors, midwives, or the health service, and will not impact the care that you are given.

6 What are the alternatives to participation?

You do not have to take part in this study to receive treatment at this hospital. Your routine pregnancy care will not change or be impacted if you decide not to take part.

7 What are the possible benefits of taking part?

This research may provide us with further insight into prevention of preterm birth and could play an integral role in changing future clinical practice. We are conducting this study to mainly check whether such a pregnancy intervention is feasible and safe, and we are not yet sure if/which aspect of lockdown measures impact preterm birth rates. As such, there may be no clear benefit for your pregnancy from your participation.

Given the COVID-19 pandemic is still ongoing, a potential benefit for anyone who is in the intervention group of the study is that they may be less likely to contract the virus given they will be adhering to established viral mitigation measures, that is, restrictions to travel/social distancing/physical contact and recommendations regarding hygiene/face coverings known to prevent transmission.

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

We anticipate that the main risks associated with participating in this study are feelings of social isolation and perhaps decreased social support in those who are a part of the pregnancy intervention group. You may also find that the additional restrictive measures imposed may make it more difficult to perform your routine tasks, for example, you may have to shop online as opposed to in store for non-essential items. If you are asked to restrict your activities and minimise your social contacts, your partner and/or other household contacts may feel burdened with additional responsibilities such as increased chores or tasks associated with looking after your other children.

In this event, please inform a member of the research team and we will guide you in accessing the appropriate services such as seeing your GP, counselling services and/or speaking with organisation such as Lifeline (13 11 14). You are welcome to contact the researchers at any time via email or phone to discuss this further and you can withdraw from the study at any stage. You will not incur any risk if you choose to withdraw.

9 What if new information arises during this research project?

There are times where during a research project, new information may become available about the condition we are investigating. If this was to occur, the researcher will inform you about it and discuss whether you would like to continue to take part in the study. If you decided that you would still like to be a part of the study, we may ask you to sign an updated consent form.

If we discover new information that leads us to believe that it would be in your best interests to withdraw from the study, the researcher will discuss the reasons with you.

10 What if I withdraw from this research project?

You can withdraw from the study at any stage. If you decide to withdraw, please let a member of the research team know via email or phone. We will discuss the reason for withdrawal with you so we can determine if there are any specific health risks or requirements linked to withdrawing.

11 Could this research project be stopped unexpectedly?

This study could be stopped unexpectedly for several reasons. For example, if we found that there were unacceptable adverse effects or new information became available regarding the effect of lockdown measures on the rate of preterm birth.

12 What happens when the research project ends?

Once the study finishes, our team will analyse the results. If you would like to be informed of the results, please let us know and we can email you a copy. Your privacy will be protected as we will only be reporting the whole group's results, which means there is no way your individual results could be traced to you.

Part 2 How is the research project being conducted?

13 What will happen to information about me?

By signing this consent form, you are consenting for authorized members of our research team to collect, store and use relevant personal information for this study. Your information may be collected from our medical records, the actigraphy device worn on your wrist and surveys that you will have completed over the duration of the study. Any information we collect with relation to this project that could identify you will be kept confidential to protect your privacy, on a secure, password protected computer system at the relevant health service. Only authorised members of the research team will have access to this information, and it will only be used for the purpose of research. This information can only be disclosed with your permission or if required to do so by law.

We anticipate that the results of this study will be published in a peer-reviewed journal and presented at various forums such as medical conferences when appropriate. Information will only be presented in a de-identified manner, which means you will not be identified, unless you give us permission. As per Monash Health research policy, we will store your information for 15 years. After this period, we may dispose of all the information in a safe and secure manner such as shredding paper records and permanently deleting any electronic records.

Information regarding your participation in this trial will be recorded in your health record.

As per Australian and/or Victorian privacy and other relevant laws, you have the right to request access to the information the research team collects and stores. You also have the right to request that any information you disagree with be rectified. If you would like to take part in our study and would like access to the information we collect, please feel free to contact a member of the research team (their details are at the end of this document).

14 Complaints and Compensation

If you suffer from a medical condition or complication because of this trial, please contact a member of the research team immediately so that we can assist in arranging the appropriate medical treatment. Any treatment you require should be free of charge if you are a Medicare card holder and attend an Australian public hospital as a public patient.

15 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 Monash Health HREC.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2018)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

16 Further information and who to contact

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

If you want any further information concerning this project or if you develop any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor as below:

Principal Study Doctor

Name	A/Prof Daniel Rolnik
Position	Consultant Obstetrician and Gynaecologist, Monash Health
Telephone	0452 105 585
Email	daniel.rolnik@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 name	Monash Health Human Research Ethics Committee
HREC Executive Officer	HREC Executive Officer
Telephone	03 9594 4611
Email	Research@monashhealth.org

Consent Form

Title	Randomised controlled trial investigating the effect of viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women
Short Title	Viral mitigation measures and preterm birth
Project Sponsor	Monash Health
Principal Investigators	Professor Ben Mol
Associate Investigators	A/Prof Daniel Rolnik, A/Prof Atul Malhotra, Dr Shivadharshini Sridhar

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 give permission for my doctors, other health professionals, hospitals, or laboratories outside this hospital to release information to Monash Health concerning my health for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to my participation in this research project as described and understand that I am free to withdraw them at any time during the research project without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Participant's Name (please print): _____

Participant's Signature: _____ Date_____

Name of Witness*

to participant's signature (please print) _____

Signature: _____ Date: _____

* Witness is not to be the investigator, a member of the study 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 Study Doctor

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 Study Doctor

(please print): _____

Signature: _____ Date: _____

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

FORTNIGHTLY PARTICIPANT SURVEY

1. On average, how often did you wear a face covering when outside your home in a week?
    a. Never
    b. Sometimes (specify which type)
    c. Most of the time (specify which type)
    d. Always (specify which type)
2. On average, how often were you within 1.5m distance of another person who is not a household contact in a week?
    a. Never
    b. Sometimes
    c. Most of the time
    d. Always
3. On average, how often did you perform hand hygiene prior to touching your nose/mouth in a week?
    a. Never
    b. Sometime
    c. Most of the time
    d. Always
4. One average, how many times did you leave your house for activities that are not considered 'essential' in a week? Essential activities include shopping for essentials, to work/study, to give/seek care or for outside exercises.
    a. 0-5 times
    b. 5-10 times
    c. 10-20 times
    d. > 20 times
5. On average, how often did you travel beyond 5km of your place of residence in a week?
    a. 0-5 times
    b. 5-10 times
    c. 10-15 times
    d. >15 times
6. On average, how often did you leave your home between the hours of 9pm-5am for non-essential purposes in a week? Essential activities include for work/study or to seek/give care.
    a. 0-5 times
    b. 5-10 times
    c. 10-15 times
    d. >15 times
7. On average, how many visitors did you have to your home in a week, excluding an intimate partner?
    a. 0-2
    b. 2-4
    c. 4-6
    d. >6

Sleep, Mood and Quality of Life

1. How many hours of sleep are you getting each night?
    a. 2-6 hours
    b. 6-8 hours
    c. 8-10 hours
    d. >10 hours
2. How often have you felt sad/low for no good reason?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
3. How often have you felt anxious or panicky for no good reason?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
4. How often have you looked forward with enjoyment to things?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
5. How often have you felt like you were having trouble coping with things?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
6. How often have you felt that you have someone with whom you can share your joys, sorrows and anxieties with?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
7. How often have you felt that you have someone to count on when you need help?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
8. How often have you felt unable to cope with performing your usually day to day activities alongside your pregnancy?
    a. Never
    b. Sometimes
    c. Most of the time
    d. All of the time
9. How satisfied do you feel with your social life right now?
    a. No satisfaction
    b. Some satisfaction
    c. Mostly satisfaction

d. Complete satisfaction

Study Experience (For intervention group only, included as part of the final survey)

1. How difficult do you feel it was to comply with the lockdown measures in this study?
    a. Very difficult
    b. Mostly difficult
    c. Neither difficult nor easy
    d. Mostly easy
    e. Very easy
2. Which measure was the most difficult to comply with?
    a. Maintaining 1.5m distance between yourself and another individual
    b. Wearing a face covering
    c. Performing hand hygiene prior to touching your nose/mouth
    d. Remaining withing 5km of your residence
    e. Remaining at home between 9pm-5am, except for essential purposes (work/study or to seek/give care)
    f. Only leaving home for essential purposes (work or study, to seek/give care or for outside exercise)
    g. Refraining from having visitors to your home except for an intimate partner
3. How disruptive were these lockdown measures to your day-to-day life?
    a. Very disruptive
    b. Mostly disruptive
    c. Somewhat disruptive
    d. Not disruptive at all
4. If we could definitively prove that lockdown decreased the risk of preterm birth, do you feel that this is a reasonable set of measures to ask pregnant women to comply with?
    a. Yes
    b. No
5. Do you feel that the lockdown measures you were required to comply with put a strain on your partner/friends/family?
    a. Yes (specify why/how)
    b. No
6. Was the wrist device you were asked to wear comfortable?
    a. Yes
    b. No
7. Did you feel it was reasonable to ask pregnant women to wear the wrist device for the duration of their time in the trial?
    a. Yes
    b. No
8. Were there any reasons why you felt you could not wear the device or had to remove it for extended periods of time (e.g more than 3 hours)?
    a. Yes (please specify when/why)
    b. No
9. Please feel free to add any other thoughts/comments/concerns about your experience in this study:
    a. ……..

iPREM Pilot Trial: Reporting Checklist

		Reporting Item	Page Number
Administrative information			
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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 15
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2

Roles and responsibilities: sponsor and funder	#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 – sponsor/funders did not play any roles in study design
Roles and responsibilities: committees	#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)	12, 13
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	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5, 6
Objectives	#7	Specific objectives or hypotheses	6

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, non-inferiority, exploratory)	6
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	7
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)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in	N/A - the intervention will not be modified for any given trial participant.

		response to harms, participant request, or improving / worsening disease)	
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A - as this is a feasability trial, there is no specific adherence recommendations given this is what we are measuring in the first instance.
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	9-11
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 (see Figure)	8, 9

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	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
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	7
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	7

Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A - participants and healthcare staff are not blinded. There are no circumstances under which emergency unblinding of data collectors/analysts will be required.
Methods: Data collection, management, and analysis			
Data collection plan	#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,	10, 11

		laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	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	12
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	13, 14
Statistics: outcomes	#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	11, 12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11, 12

Statistics: analysis population and missing data	#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)	11, 12
Methods:			
Monitoring			
Data monitoring: formal committee	#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	12, 13
Data monitoring: interim analysis	#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	13
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	12

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
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)	11
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
Consent or assent: ancillary studies	#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	13, 14

		confidentiality before, during, and after the trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13, 14
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	13
Dissemination policy: trial results	#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	13, 14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	14
Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A

reproducible research			

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	See supplementary material
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

Notes:

- 5c: N/A - sponsor/funders did not play any roles in study design
- 11b: N/A - the intervention will not be modified for any given trial participant.
- 11c: N/A - as this is a feasability trial, there is no specific adherence recommendations given this is what we are measuring in the first instance.
- 17b: N/A - participants and healthcare staff are not blinded. There are no circumstances under which emergency unblinding of data collectors/analysts will be required. The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 24. April 2023 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai