**PROTOCOL**

**(August 2023)**

**A pilot feasibility randomised controlled trial investigating the effect of viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women**

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| Protocol ID  | RES-22-0000-122A |
| Short title  | iPREM (Pilot)  |
| Version  | 5.0 |
| Date  | August 2023 |
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# SUMMARY

On March 11th, 2020, the World Health Organization declared the outbreak of SARS-CoV-2 to be a pandemic. With case numbers rising sharply, Australian state and territory governments began introducing restriction measures including limitations on social gatherings, closure of non-essential services and social distancing rules with the aim of mitigating spread of the virus. The Victorian state government imposed a less stringent set of restrictions in March 2020, followed by a period of eased restricted and then a second, harsher set of restrictions in July 2020.

It has been observed that there has been a reduction in the rate of preterm birth in women exposed to restriction measures implemented to mitigate SARS-CoV-2 transmission; an effect that is more pronounced in women who have previously experienced a preterm birth.

We propose a two-arm randomized controlled feasibility clinical trial. We will study pregnant women who are enrolled in the antenatal clinics and who have previously had a preterm birth (<34 weeks). Eligible participants will be randomized into two groups: the intervention group, where participants will be required to adhere to restriction measures originally imposed to mitigate transmission of the SARS-CoV-2 virus until birth or the control group, where participants will undergo standard pregnancy care.

The primary outcome of this trial will be feasibility, which will be assessed by measuring patient eligibility rate, recruitment rate, compliance rate and data completion rate. The secondary outcome measures of this trial will be the rate of preterm birth (<34 weeks), maternal quality of life and pregnancy outcomes. We will aim to recruit up to 100 pregnant women, 50 of whom will be randomized to the intervention and 50 of whom will be randomized to the control group.

The aim of this study is to establish feasibility and we acknowledge that the sample size is not significant enough to prove an effect on the rate of preterm birth. This study will establish a foundation upon which to conduct a larger randomized controlled trial, investigating the effects of restriction measures on the reduction of the rate of preterm birth and therefore play a role in preventing the significant health and economic consequences of preterm birth.

# 1. INTRODUCTION AND RATIONALE

Preterm birth, defined as delivery prior to 37 weeks of 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 of preterm births being 33.3 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]. It is categorized as early preterm (<34 weeks), very preterm (28 to 32 weeks) and extremely preterm (<28 weeks) and an increasing degree of prematurity is known to correlate with a greater risk of complications. Of the infants that survive, there is in increased risk of life long consequences including cerebral palsy, retinopathies, neurodevelopmental delay and chronic lung disease [4].

Aside from the physical and mental health consequences of prematurity for both the infant and their families, there is also a significant economic impact. 72% of preterm infants will need admission to the Neonatal Intensive Care Unit (compared to 10% of term infants) where the average length of admission is 28 days and the cost per day is almost $2000 [2, 5]. In comparison to mothers of term infants in the post partum period, mothers of preterm infants take longer to return to work, have a lower medium income and increased out of pocket costs related to healthcare [6].

The exact causality of preterm birth remains unknown, however risk factors include previous preterm birth, maternal age, smoking, multiple gestation, alcohol intake, maternal medical disorders such as gestational diabetes, maternal literacy level and social disadvantage [3]. Although we now have multiple methods with which to manage high risk women including progesterone treatments, aspirin and cervical cerclage, overall preterm birth rates have continued to rise in most industrialised countries [7, 8].

The outbreak of the SARS-CoV-2 brought the world to a standstill, having drastic social and economic impacts. The first Australian case of the novel SARS-CoV-2 virus was detected in Victoria on January 25th, 2020 and by March, each Australian state and territory was beginning to introduce measures to mitigate spread of the virus [9]. This included maintaining social distancing, limiting social contacts, wearing face masks and performing hand hygiene.

Unexpectedly, it has been observed around the world that pregnant women exposed to mitigation measures for the SARS-CoV-2 virus have had a decrease preterm birth rate. Several studies have noted a reduction in preterm birth rates by 20-30%, with this effect being more pronounced in very 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 experience a preterm birth (RR 0.93, 95% CI 0.63-1.28; p = 0.714) [13].

We hypothesize that in women with a previous preterm birth (i.e birth <34 weeks), a pregnancy intervention mimicking SARS-CoV-2 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:

* Reduced rates of infection due to social distancing and hygiene measures
* Reduced mobility and activity levels
* Reduced stress levels
* Reduce noise and air pollution
* Reduced medical interventions

We have designed a pilot randomised controlled trial to assess the feasibility of implementing a pregnancy intervention that mimicks SARS-CoV-2 mitigation measures in pregnant women with a previous preterm birth. Our study’s main aim is to evaluate feasibility, however, we will also note the effect of the intervention on preterm birth rates as a secondary outcome.

It is is important to to conduct this study given preterm birth continues to have a significant medical and financial impact on families. Although we know some risk factors for preterm birth, many are unexplained and therefore it is difficult to implement prevention measures when causality remains undetermined [3]. Observational studies have demonstrated that SARS-CoV-2 mitigation measures have an effect on preterm birth rates, however findings are inconsistent, it is unclear which aspect of these measures contribute to the phenomenon and to our knowledge, there have been no randomized controlled trials that have further investigated this to establish causality.

# 2. OBJECTIVE

The aim of this study is to study the effect of mitigation measures to prevent the transmission of COVID-19 on the incidence of preterm birth in pregnant women who have previously had a preterm birth (<34 weeks).

The primary objective of this study will be to investigate the feasibility of the intervention and the feasibility of the trial.

The secondary objective will be to evaluate the impact of the restriction measures on incidence of preterm birth in women who have previously experienced a preterm birth, maternal quality of life and pregnancy outcomes.

# 3. STUDY DESIGN

A two-arm open-label randomized controlled clinical trial. The flowchart of the study is shown in Figure 1.

Patient recruitment

No

Eligibility Assesment

Informed consent

Yes

Standard pregnancy care

Routine treatment

Exposure to restriction measures

Follow-up

Figure 1. Flowchart.

1 Intervention

2 Control

# 4. STUDY POPULATION

## 4.1 Inclusion and exclusion criteria

Inclusion Criteria

* Adult pregnant women (singleton or multiple gestation) who are at ‘high risk’ of having a preterm birth where ‘high-risk’ will be defined as pregnant women who have had a previous preterm birth between 22-34 weeks gestation, either spontaneously or due to iatrogenic delivery.

Exclusion criteria

* We will exclude pregnant women carrying a foetus with one or more major congenital abnormalities.
* We will exclude pregnant women under the age of 18.
* We will exclude pregnant women carrying a multiple gestation if they have not had a previous preterm birth.

## 4.2 Sample size calculation

Given the primary objective of this trial is to establish feasibility, we will aim to recruit up to 100 ‘high-risk’ pregnant women, 50 of whom will be randomised to the intervention group and 50 of whom will be randomised to the control group.

# 5. RECRUITMENT, RANDOMIZATION, INTERVENTIONS, AND PROCEDURES

## 5.1 Recruitment

Pregnant women who are enrolled in 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 flagging eligible women. We will also debrief clinicians at the clinic on the study details so that they can refer any eligible patients we may have missed in our initial screening process and display flyers advertising the study on the rooms of the clinic so women who feel they are eligible can also contact the research team themselves. When an eligible woman presents to the clinic, we will ask her treating clinician to briefly explain the study, provide her with a patient invitation form and provide her contact details to the research team with her consent. A member of our research team will approach said interested 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.

In the instance that an eligible patient is attending the clinic via telehealth, we ask that the treating clinician explain the study briefly to her and provide the research team with her contact details (if she is interested) with her consent. The research team will contact the interested participant via phone/email to explain the study in further detail and email the patient a patient information consent form to be signed and returned.

No members of the research team are involved in the care of potential participants at the site of recruitment, ensuring there is no unequal or dependent relationship.

## 5.2 Randomization

Participants will be randomized to either the intervention group, where they will be instructed to adhere to restriction measures initially imposed to mitigate Sars-CoV-2 transmission, or the control group where they will undergo standard pregnancy care. Randomization and allocation processes will be performed on the first day of the trial, through a computer-generated randomization list in RedCap. Redcap is a secure, web-based data collection and management software that meets Health Inurance Portability and Accountability Act (HIPAA) compliance standards[14, 15].

This study will not be blinded to nurses, midwives, doctors, participants or investigators. The member of the research team that collects study outcome data will be blinded to the group that the participant was allocated to.

## 5.3 Interventions

Intervention Group

This pregnancy intervention is designed to mimic the stage 3 and 4 SARS-CoV-2 virus mititgation measures implemented in metropolitan Melbourne, Australia. Study participants will be asked to comply with the follow measures for the duration of the intervention:

1. Study participants will be asked to try to minimise the number of visitors to their home and refrain from attending large social gatherings where possible.
2. Study participants will be asked to 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. Study participants will be instructed to 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.

Control Group

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

## 5.4 Study procedures

Participants will be recruited two weeks prior to the gestational age at which the study participant’s previous preterm birth occurred (i.e. if someone delivered in her previous pregnancy at 32+3 weeks, the intervention will start at 30+3 weeks). 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 30+6 weeks gestation. It will be conducted for six weeks (i.e two weeks prior and four weeks post the gestational age of the previous preterm birth) or until 34 weeks of gestation or until birth, whichever comes first.

Participants will be required to complete short surveys (which will be developed through REDCap) to assess their compliance with the intervention, activities, mood and quality of life at baseline and then on a fortnightly basis for the duration of the study.

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 (figure 2). 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.



*Figure 2. Actigraphy Device.*

# 6. METHODS

## 6.1 Study endpoints

Primary outcome

Primary Outcome: Feasibility of this study.

We will measure feasibility using the following criteria alongside targets that will establish whether a larger trial would be feasible to conduct:

* Patient eligibility rate
	+ Measured as the proportion of eligible women screened at antenatal clinics who provide informed consent.
	+ We will set a target of at least 50%
* Patient recruitment rate
	+ The proportion of eligible pregnant women who arerandomized.
	+ We will set a target of at least 50%
* Compliance rate
	+ The proportion of participants in the intervention group who are considered to have good compliance with the intervention.
	+ Compliance will be measured using subjective and objective measures. Participants will be asked to fill out short, online questionnaires on a fortnightly basis and wear an actigraphy device (figure 2) for the duration of their time in the trial.
	+ We will set a target of at least 75%.
* Data completion rate
	+ This will be measured as the proportion of final surveys completed (i.e the survey that is conducted after the end of the intervention)
	+ We will set a target of at least 75%.

Secondary outcomes

* Incidence of preterm birth (<34 weeks)
* Maternal quality of life
	+ This will be a measure of health-related quality of life of women via fortnightly surveys based on previously validated questionnaires, including the mental health questionnaire, Depression, Anxiety and Stress Scale (DASS-21) as well as the Edinburgh Postnatal Depression Score.
* Pregnancy Outcomes
	+ We will record pregnancy duration, incidence of stillbirth, incidence of iatrogenic and spontaneous delivery
	+ Other pregnancy, birth, and maternal postnatal outcomes
* Actigraphy Device Outcomes
	+ We will collect raw actigraphy device data to determine physical activity patterns, sleep-wake cycle and compliance with wearing the device for the duration of the trial.

## 6.2 Subject informed consent

Pregnant women who are enrolled in 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. When an eligible woman presents to the clinic, we will ask her treating clinician to briefly explain the study, provide her with a patient invitation form and provide her contact details to the research team with her consent. A member of our research team will approach eligible patients and explain trial details prior to the start date. Prospective participants will be given written information about the trial and 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 consent form. We will ensure to obtain and store an individual record of all non-recruited patients, including their reasons for exclusion.

## 6.3 Withdrawal of consent for participation

All participants will have the right to decline participation and/or withdraw their consent at any time during the study process. Their decision to do so will not affect any conventional clinical treatment offered to them nor will it impact their relationship with any health professionals.

## 6.4 Duration of the study

The recruitment in the study centre will start in April 2022 and will continue until the needed number of participants is included, anticipated until April 2023. The study duration is estimated to be one year.

## 6.5 Statistical analysis

*Baseline and outcome data*

Baseline continuous covariates will be expressed 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 section 6.1.

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 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.

*Missing data and sensitivity analysis*

The primary analysis will be conducted on an available-case fashion. We will first perform analysis by excluding missing values for any missing values in baseline characteristics. Following this, we will perform multiple imputation by chained equations with ten imputed datasets to account for missing values on covariates, and sensitivity analysis will be performed to investigate the effect of missing data on secondary outcomes of the study. Participants with missing outcome data due to loss to follow-up will be excluded from analyses.

*Subgroup analysis*

Subgroup analyses will be performed to investigate subgroup effects in women with a previous spontaneous versus iatrogenic preterm birth, smokers versus non-smokers, and women with normal versus increased BMI. Effect modification will be investigation with the use of interaction terms in the logistic regression models, and by inspection of forest plots of subgroups.

## 6.6 Data and Safety Monitoring Board

A data safety and monitoring board (DSMB) will be created, whose primary role will be to review the study, the data generated and ensure safety of all participants while the scientific goals of the study are met. If any significants risks or benefits are uncovered during the study or the study cannot be concluded successfully, the DSMB will be responsible for determining its appropriate termination.

The DSMB will be made of a chairperson and two voting members, all of whom will be impartial and independent of investigator(s). Members of the DSMB will not have any vested financial, scientific or other conflicts of interest with this trial. The DSMB will conduct regular teleconferences prior to the commencement of the study to review the protocol with regards to ethics and safety standards as well as ensure integrity of data in view of the original protocol. During the trial the DSMB will ensure to review the study’s progress on a regular basis, investigate any adverse events, maintain ongoing safety of participants and call for premature termination of the study if required.

|  |  |
| --- | --- |
| A/Prof Peter Temple-Smith(Senior Research Fellow in Obstetrics & Gynecology, School of Clinical Sciences at Monash Health) | Chair of DSMB |
| Dr Miranda Davies-Tuck(Perinaral Epidemiologist, Monash Health) | Member of DSMB |
| Dr Douglas Blank(Consultant Neonatologist, Monash Health) | Member of DSMB |

## 6.7 Interim analysis

An interim analysis will be conducted after the recruitment of 50 participants i.e half the number of participants planned for this feasibility trial. The DSMB will be required to assess the ongoing safety of the trial, evaluate any adverse events and will have the ability to suspend or terminate the study if required.

# 7. SAFETY REPORTING

## 7.1 WMO event

If a significant event were to occur, where participation in the study posed a greater disadvantage than what had been anticipated by the initial research propososal, the investigator will inform the accredited medical research ethics committee (MREC). The study will be suspended until further review is conducted by MREC (unless suspension would further jeopardize the participant’s health). The investigor will ensure to keep all participants appropriately informed of any such event and the relevant outcomes.

## 7.2 Adverse and serious adverse events

An adverse event (AE) is defined as any undesirable experience that a trial subject may experience during the trial, regardless of the relationship of said event to the intervention. A record will be kept of all AEs reported by participants or observed by investigators.

A serious adverse event (SAE) is defined as any unfortunate medical occurrence that results in death, is considered life-threatening, results in hospital admission and/or prolongs the patient’s hospital stay, results in significant and/or persisting disability/incapacity or is a new event as a result of the trial that is likely to negatively affect the trial participant. The DSMB and relevant accredited Medical Education Technology Committee (METC) who approved the protocol will be notified of all SAEs.

## 7.3 Follow-up of adverse events

All AEs will be followed up until they have resolved or the participant is stabilized. Depending on the AE, follow up may include referral to a physician for further evaluation and/or additional tests/treatments as indicated.

# 8. ETHICAL CONSIDERATIONS

## 8.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (World Medical Association Declaration Of Helsinki Ethical Principles for Medical Research Involving Human Subjects Version Edinburgh, Scotland, October 2000, with Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002 end Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

## 8.2 Recruitment and consent

The investigor will ensure that each participant is informed of the nature of the study, its purpose, the procedures involve, the potential benefits and/or risks as well as the expected duration. Subjects will be made aware that their participation is entirely voluntary and that they are free to withdraw at any time for any reason. The investigator will also inform participants that withdrawal of consent will not affect their relationship with their physician or their right to appropriate medical treatment.

## 8.3 Privacy

A code number will be assigned to each subject which will be consistent with their allocated intervention. This number will be displayed on all report forms in order to maintain confidentiality.

## 8.4 Benefits and risks assessment, group relatedness

As the SARS-CoV-2 pandemic is ongoing, patients randomized to the intervention group are less likely to contract the virus given they are adhering the established mitigation measures shown to prevent transmission.

We anticipate that the main risks associated with participating in this study will be feelings of social isolation as well as perceived decrease in social support in those randomized to the intervention group. Participants may also find it more difficult to perform their routine tasks, for example, they may have to shop online for non-essential items as opposed to in store. Given that these participants will be required to restrict activities and minimize social contacts, their partners and/or household contacts may feel more burdened as they may have to take on additional responsibilities such as household chores or child care**.** Participants will be encouraged to inform the research team if this occurs and the team will ensure to guide the participant in accessing relevant services such as seeing their GP, accessing counselling services and/or contacting organisations such as Lifeline.

# 9. FEASIBILITY OF STUDY

One of the proposed study centre’s antenatal clinic covers a catchment area with a population of more than 1 million inhabitants and has the advantage of delivering both maternity and paediatric services. With numerous high risk pregnant women being managed through this service, adequate participant enrolement is ensured.

# 10. ADMINISTRATIVE ASPECTS AND PUBLICATION

## 10.1 Handling and storage of data and documents

Data for this trial will be collected from the relevant online medical records system (such as demographic data, history of preterm birth) as well as via questionnaires completed by participants following informed consent. Online questionnaires will be developed using REDCap, which as mentioned previously, is a secure, web based data collection and management software that is in compliance with HIPAA standards.

Our research team will be required to receive training to ensure they master the details of the trial prior to administering it, understand the randomization methods and the case report form. A clinical data collection system (EDC) will be used to collect the aforementioned characteristics.

After eligible participants are recruited, the data input will be completed by trained assessors. They will log in to a secure data portal and upload data to the eCRF with the personal trial ID of each participant. The data will only be accessible to authorized members of the research team.

The data will be stored for 15 years. Following this, all electronic records will be securely disposed off through permanent deletion and any paper records will be shredded.

## 10.2 Annual progress report

We anticipate that the recruitment for this pilot study will take around 9-12 months and the intervention for each individual participant should be approximately six weeks duration. The study should therefore be completed within a maximum of two years and therefore an annual progress report will not be required.

## 10.3 End of study report

The accredited METC and the competent authority will be informed of the study’s end date within a period of 90 days by the principal investigator. The study end date will be defined as when the last participant has given birth. If a study needs to terminated early, the principal investigator will ensure to inform the accredited METC within 15 days and specify the reasons for premature termination.

## 10.4 Public disclosure and publication policy

Participants and/or the public will not be involved in formulating the research question, design of the study or implementation of the trial. The participants will be emailed the results of the study. The principal investigator will submit the results of the study for publication in a peer-reviewed journals and for presentation in medical conferences when appropriate.

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