PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Sridhar, Shivadharshini; Mol, Ben; Hodges, Ryan; Palmer, Kirsten; Sundram, Suresh; de Carvalho Pacagnella, Rodolfo; Souza, Renato; Barbosa-Junior, Francisco; Mackin, David; Said, Joanne; Rolnik, Daniel; Malhotra, Atul

VERSION 1 – REVIEW

REVIEWER	Lombard, Carl University of Stellenbosch, Division of Epidemiology and Biostatistics
REVIEW RETURNED	08-Jun-2023

GENERAL COMMENTS	This is an interesting study evolving from the observational studies done on incidence of pre-term births during Covid restrictions in this setting. Abstract: Elements of the feasibility outcome are patient eligibility rate and recruitment rate. Therefore, the study population which will deliver used to determine these outcomes have to be described in some way. They are as important for assessing feasibility as is the participants who are randomized. Intervention: There is no indication of how the standard pregnancy care will be handled/ conducted/adapted in the intervention group as well as possible emergencies. Line 11-16: Here it is stated as if all participants will be completing the online survey. However, when you look at the detail of the survey questions - many questions only pertain to the intervention groups. Will these 2 weekly surveys be done by both groups (which would make sense) or just by the participants of the intervention group? Given the nature of some of the exposure question in the questionnaire this can be considered as a co-intervention since it sensitizes the participants to limiting their exposures. Randomisation: Given the outline of known risk factors in lines 29-25 no stratification on one or more of these factors were considered. Why was this the case?

	Secondary data collection and other data collection: There is no outline on how, by whom, when and where this data will be collected. Partner: It would be useful to get the acceptability of the intervention from the participants partner since the intervention will also affect their daily life. Tracking watch: It is not clear if the control women will also be wearing a watch to track activities and sleeping patterns. Is this the case? Sample size: Even though this is a pilot study there is no discussion or indication of why a sample size of 100 participants (n=50 in the intervention group) would be adequate for the primary outcome and judging the trial success against the stated targets.

REVIEWER	Barut, Adil Somali-Mogadishu Recep Tayyip Erdoğan Research and Training Hospital
REVIEW RETURNED	13-Jun-2023

GENERAL COMMENTS	this is a ethics committee approval. it is not revieW.

REVIEWER	Zeleke, Eden Ohio State University Global One Health Initiatives
REVIEW RETURNED	24-Jul-2023

GENERAL COMMENTS	1. Title: Since the primary objective is feasibility, I would edit the title as "Feasibility of viral transmission mitigation measures on the incidence of preterm birth in high risk pregnant women" 2. Abstract: Ethics and Dissemination section, you discussed about study period and commencement date of data collection which should move to method and analysis section. 3. Article summary: Please elaborate the strength and limitation of using randomization than only saying "This study is a randomized controlled trial." 4.Methos and analysis: I don't see the study area description, you only write it is multi site study, what proportion of data collected from each site? How did you select those sites? The objective of the study should be written separately not under method section. Sample size: How did you come up with this amount of sample size? Patient population: Why did you exclude those pregnant women who are less than 18 years old ? Recruitment: I would show the recruitment process by figure. Interventions: Please define stage 3 and 4 COVID 19 virus mitigation measures? For those participants who don't read and write, the person who gonna fill the short survey is not explained. Outcomes: For those criteria used to measure feasibility, how did you come up with those cutting %ages? Data Safety Monitoring Board: What other experts should be included in the member?

VERSION 1 – AUTHOR RESPONSE

Reviewer #1 | Point #1	
A	Abstract: Elements of the feasibility outcome are patient eligibility rate and recruitment rate. Therefore, the study population which will deliver used to determine these outcomes have to be described in some way. They are as important for assessing feasibility as is the participants who are randomized.
B	We thank the reviewer for their comment. Please note that we have now specified the study population further in the Methods and Analysis section of the abstract.
C	Page 2; Line 11-13
D	"One hundred pregnant women, enrolled in antenatal clinics at tertiary maternity centres in Melbourne, Australia, who have had a previous preterm birth between 22-34 weeks gestation will be recruited."

Reviewer #1 | Point #2	
A	Intervention: There is no indication of how the standard pregnancy care will be handled/ conducted/adapted in the intervention group as well as possible emergencies.
B	Thank you for requesting this clarification. There will be no change to standard pregnancy care in the intervention group as advised by their antenatal care team as this is primarily a feasibility trial, and we do not want to cause further stress or harm by disrupting antenatal care for women who are already deemed high risk of preterm birth and required to make multiple lifestyle changes as part of the intervention group. We have specified that women do not have to comply with intervention measures in case of emergencies such as if they need to seek/give care and specified that they can leave their home for safety purposes. We have also added a definition for standard pregnancy care
C	Page 9; Line 23-25. Page 9; Line 29-31
D	"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)." "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."

Reviewer #1 | Point #3	
A	Line 11-16: Here it is stated as if all participants will be completing the online survey. However, when you look at the detail of the survey questions - many questions only pertain to the

	intervention groups. Will these 2 weekly surveys be done by both groups (which would make sense) or just by the participants of the intervention group? Given the nature of some of the exposure question in the questionnaire this can be considered as a co-intervention since it sensitizes the participants to limiting their exposures.
B	We are grateful to the reviewer for bringing this to our attention. Please note that all participants will be required to complete the fortnightly survey – the line has been modified to reflect this as below. The questions are specific to the hygiene, social contacts and physical activities that are restricted in the intervention group; however, we are asking the control group to also answer the same questions to understand what hygiene measures, social contacts, and physical activities these women may be performing at baseline. This is to ascertain whether there is a discernible difference in these lifestyle measures between the control and intervention group as some women may continue to lead a more restricted lifestyle at baseline, especially when COVID infections continue to affect the community in which the study is taking place.
C	Page 10; Line 15-18
D	"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)."

Reviewer #1 | Point #4	
A	Randomisation: Given the outline of known risk factors in lines 29-25 no stratification on one or more of these factors were considered. Why was this the case?
B	We thank the reviewer for this insightful question. Given this is primarily a feasibility trial and the fact that we were unsure what our recruitment rate would be (as it is the first of its kind), we chose to use block randomisation. We felt stratification would not be possible because this is a time sensitive trial and participants start/finish their time in their trial at different time points. Therefore, we cannot identify all participants prior to the start of their time in the trial to randomise them into appropriate strata. We would certainly consider utilising stratified randomisation in a larger, randomised controlled trial where we have a better understanding of the recruitment rate and the primary outcome is estimating the effect of viral mitigation measures on preterm birth rates.
C	-
D	-

Reviewer #1 | Point #5	
A	Secondary data collection and other data collection: There is no outline on how, by whom, when and where this data will be collected.

B	We thank the reviewer for this comment. Please note we have now specified this in the main document.
C	Page 12; Line 27-30
D	“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.”

Reviewer #1 | Point #6	
A	Partner: It would be useful to get the acceptability of the intervention from the participants partner since the intervention will also affect their daily life.
B	We are grateful to the reviewer for raising this point as it is certainly an intervention that may affect both the participant and their support persons. Please note that as part of the final survey, we ask participants who were assigned to the intervention group to specify how the intervention affected their support people. We are in the process of expanding our team and once we have capacity will certainly considering adding a component to assess partner/support people acceptability.
C	Supplementary Material – Page 14; Question 5
D	-

Reviewer #1 | Point #7	
A	Tracking watch: It is not clear if the control women will also be wearing a watch to track activities and sleeping patterns. Is this the case?
B	We thank the reviewer for requesting this clarification. All participants will be asked to wear an actigraphy device so that we can collect and compare objective physical activity and sleep data between the two groups. Please note we have now specified this in the main document.
C	Page 10; Line 20-22
D	“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.”

Reviewer #1 | Point #8	
A	Even though this is a pilot study there is no discussion or indication of why a sample size of 100 participants (n=50 in the intervention group) would be adequate for the primary outcome and judging the trial success against the stated targets.
B	We thank the reviewer for requesting this clarification. At the initial recruitment site, we estimated that there may be approximately 150-200 women eligible to participate based on the number of women who give birth to preterm babies < 34 weeks annually at this health

	network. After discussion with the research team, consisting of both obstetricians and neonatologists, we chose a sample size of 100 (half of the eligible population) to determine feasibility as we felt that this would be representative of the overall group. Please note if have now clarified this further under 'Sample Size'.
C	Page 7; Line 8-11
D	"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."

Reviewer #3 | Point #1	
A	Title: Since the primary objective is feasibility, I would edit the title as "Feasibility of viral transmission mitigation measures on the incidence of preterm birth in high-risk pregnant women"
B	We thank the reviewer for this suggestion and have altered the title accordingly.
C	Title
D	"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"

Reviewer #3 | Point #2	
A	Abstract: Ethics and Dissemination section, you discussed about study period and commencement date of data collection which should move to method and analysis section.
B	We thank the reviewer for this comment. We have moved this statement to the Recruitment section under Methods and Analysis. Please note we have also modified the recruitment duration from 12-18 months to 18-24 months. This is because setting up recruitment at our second site is taking longer than expected.
C	Page 8; Line 16-17
D	"Recruitment commenced in June 2022 and is expected to take around 18-24 months for completion."

Reviewer #3 | Point #3	
A	Article summary: Please elaborate the strength and limitation of using randomization than only saying "This study is a randomized controlled trial."
B	We thank the reviewer for this comment. We feel that the rigorous study design of a randomised controlled trial is a strength of this study as all previous research in this area that we are aware of is observational. We have modified the Strengths and Limitations section of the article to reflect the same. Please see response to Editor, Point #2.
C	-

D	-

Reviewer #3 | Point #4	
A	Methods and analysis: I don't see the study area description, you only write it is multi site study, what proportion of data collected from each site? How did you select those sites?
B	We thank the reviewer for this comment. Please note that we have added a description of the study area under the Study Design section.
C	Page 5; Line 25-26
D	“This is a multi-site, two-arm open-label randomised controlled clinical trial that will be conducted across tertiary maternity centres in Melbourne, Australia.”

Reviewer #3 | Point #5	
A	Methods and Analysis: The objective of the study should be written separately not under method section.
B	We thank the reviewer for this comment. Please note that we have created a separate section for the aim of the study after the Introduction.
C	Page 5; Line 19-21
D	“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.”

Reviewer #3 | Point #6	
A	Sample size: How did you come up with this amount of sample size?
B	We are grateful to reviewer for this comment. Please note we have now added an explanation for the selection of sample size as per the response to Reviewer #1, Point #8.
C	-
D	-

Reviewer #3 | Point #7	
A	Patient population: Why did you exclude those pregnant women who are less than 18 years old ?
B	We thank the reviewer for requesting this clarification. We chose to exclude pregnant women under the age of 18 as this is a pilot feasibility trial and part of the study is understanding the initial barriers and challenges that pregnant women in the intervention group may face. Young mothers already face multiple challenges, tend to require more support and have more social contacts (i.e they may still be attending school). As such, we felt that without appropriate insight into the challenges faced by women taking part in this trial, it would not be appropriate to open up the trial to such a vulnerable group of women. We also felt that they would make up a very

	small subset of the study population as a requirement for eligibility is having had a previous preterm baby < 34 weeks gestation. We will certainly consider including pregnant women under 18 years old once we have a better understanding of the acceptability of the study.
C	-
D	-

Reviewer #3 | Point #8	
A	Recruitment: I would show the recruitment process by figure.
B	We thank the reviewer for this suggestion. We have added a figure showing the study design, including recruitment and randomisation process under the Study Design section.
C	Page 5; 28 (See figures document)
D	-

Reviewer #3 | Point #9	
A	Interventions: Please define stage 3 and 4 COVID 19 virus mitigation measures?
B	We thank the reviewer for requesting this clarification and have included a statement explaining Stage 3 and 4 restrictions.
C	Page 8; Line 30-33
D	“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.”

Reviewer #3 | Point #10	
A	For those participants who don't read and write, the person who gonna fill the short survey is not explained.
B	We thank the reviewer for raising this point. Please note that as this is a pilot feasibility trial, we are currently only recruiting women who primarily speak English and can read and write. We have modified the inclusion criteria to reflect this.
C	Page 7; Line 21-22
D	“Women must primarily speak English and have the ability to read and write.”

Reviewer #3 | Point #11	
A	Outcomes: For those criteria used to measure feasibility, how did you come up with those cutting %ages?

B	We thank the reviewer for requesting this clarification. Given this is a pilot feasibility trial with no precedent, the criteria and cut offs for feasibility were determined by expert consensus with a team of obstetricians, neonatologists, senior clinician-researchers and neonatologists. For patient eligibility and recruitment rate, we set a rate of 50% as we feel that this would be reasonably representative of the study population and provide the confidence that we could recruit enough participants to conduct a larger randomised trial that will be powered to assess effectiveness of the pregnancy intervention. We set a target of 75% for compliance and data completion rate as we felt that this would be closest to adhering to lifestyle measures and requirements 'most of the time'.
C	-
D	-

Reviewer #3 | Point #12	
A	Data Safety Monitoring Board: What other experts should be included in the member?
B	We thank the reviewer for this question. At present, the Data Safety Monitoring Board (DSMB) consists of a senior research fellow in Obstetrics and Gynaecology, a consultant Neonatologist, and a perinatal epidemiologist. The trial was developed following discussion with patients and clinicians in antenatal clinics as well as in conjunction with an expert team that included psychiatrists. At present, we feel that the DSMB is made up of a reasonable team of experts who will be able to judge the safety of the study. We will consider expanding the DSMB as the trial progresses and/or if a larger randomised trial materialises.
C	-
D	-

Please note we have made the following updates to the main document as we have made changes to the trial since the original submission:

A	Please note that the recommended restrictions to the intervention group have been relaxed to increase recruitment rate. After the initial phase of recruitment, the research team noted that approximately 30% of eligible participants were consenting to take part in the trial. The majority of eligible participants who declined to take part did so as they felt the intervention was too strict. After discussion between the team, it was decided that the restrictions would be relaxed, and participants in the intervention group would no longer be required to comply with a curfew or limit travel outside their home to a 5km radius. Given our primary outcome is feasibility and our main hypotheses for the observed effect are reductions in physical activity, stress, noise/air pollution, medication intervention and/or infection rates we felt that the 5km radius and curfew were also the restrictions that were least likely to contribute to the hypotheses.
B	Page 11; Line 14-27
C	"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.”

VERSION 2 – REVIEW

REVIEWER	Lombard, Carl University of Stellenbosch, Division of Epidemiology and Biostatistics
REVIEW RETURNED	12-Oct-2023

GENERAL COMMENTS	All comments have been addressed.