PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Fast-track referral for health interventions during pregnancy: study protocol of a randomized pragmatic experimental study to reduce low birthweight in Portugal (STOP LBW)
AUTHORS	Barros, Henrique; Baia, Ines; Monjardino, Teresa; Pimenta, Pedro; Alfredo, Ana; Sorokina, Anzhela; Domingues, Rosa

VERSION 1 – REVIEW

REVIEWER	Hassen, Hamid University of Antwerp Faculty of Medicine and Health Sciences
REVIEW RETURNED	18-Jul-2021

GENERAL COMMENTS	Thank you for the opportunity to review this study protocol. The protocol summarized the rationale, objective and proposed methods and statistical analysis of the planned intervention to decrease incidence of LBW. LBW is an important public health problem in both high- and LMICs contributing to a large proportion of child morbidity and mortality. This intervention would provide great importance to decrease the incidence of LBW provided that the effectiveness is demonstrated. However, I have some issues in the methods that need to be addressed critically. Specific comments and questions are provided below. 1. The authors described in the introduction section that the incidence of LBW is disproportionately higher among vulnerable communities such as migrants. However, due to language barriers a higher proportion of migrants would be excluded from the intervention. Meaning, the intervention effect (if there) would not be generalizable to vulnerable populations, the group who need the intervention most. I suggest looking for a mechanism to include them in the intervention. 2. Teenage pregnancy needs special care during pregnancy and delivery. What motivates the authors to consider mothers aged 14 to 18 along with those above 18? This age discrepancy could have an implication in the recruitment process and adherence to the intervention. Furthermore, what is the plan of informed consent for those aged 14 to 18 years? 3. Page 9, line 35-40: “The main hypothesis….”. The authors hypothesized that interventions targeting maternal psychosocial behavioral factors might reduce incidence of LBW. However, the planned intervention is referral. Referral does not mean the participants attended the consultation sessions. In addition, if the intervention is beyond referral, detailed intervention components should be described.

	4. Study participants: including all women of any gestational age might not be a good idea. The intervention will have a different impact on the first, second and third trimester of pregnancy. Referral/consultation during late pregnancy won't have or have less impact on low birthweight. How do the authors deal with this issue? 5. The sample size calculation is very clear. However, expecting a 30% reduction in LBW seems ambiguous. The study might not be sufficiently powered to detect a 10 or 20% decrease in incidence. I would recommend to consider a lower effect size in sample size calculation. I also suggest authors plan post-hoc power analysis. 6. The authors described the intervention on page 15. Nevertheless, it is not clear whether the intervention is just 'referral' or there is a mechanism to check whether the participants attended the intended consultation. The intervention beyond referral needs to be described very well. How many sessions of consultation? How long? The intensity of consultation? What are the contents of the consultation for each risk factor? If the intervention is only referral, the primary outcome (incidence of LBW) is somewhat distant, which is less likely to have a 30% reduction. 7. Who will be responsible for the fee and other procedures for the consultation? The participant/the research team? 8. On page 15, the authors described the 'standard care' control group. The study will have multiple types of controls including consultation. How the authors will compare the effectiveness of the proposed intervention in comparison with multiple controls. Will they perform subgroup analysis? 9. Nutritional factors are important risk factors of LBW, however, they are not considered as part of the referral/intervention. 10. Line 53-54: the authors mentioned that they will use the Edinburgh Postpartum Depression Scale to assess risk of depression. However, the cutoff for this scale varies for antenatal and postnatal period (Berking V. et al, 2011). Better to comment on it. 11. Line 14-17: "The primary outcome (low birthweight) will be assessed during the first visit to the PHCU after birth"…When is the timing of first visit? The first visit might vary depending on the convenience of the women. The time should be specified clearly. Birthweight should be taken within 72 hours of delivery. 12. In page 14, line 54-57: the authors described that they will use multiple imputation if the missing is >5%. The handling of missing data depends on the pattern of missingness. MI only provides unbiased estimates under MAR assumption. Under MNAR assumption, MI won't provide unbiased estimates and hence other advanced techniques might be required. 13. Do the authors consider subgroup analysis for teenagers? I suggest performing subgroup analysis based on age group as well as different control groups. 14. The discussion is written very well. I suggest commenting on planned activities to improve sustainability of the intervention effect beyond the intervention period. Sustainability remains the main challenge of public health interventions. The continuity of the intervention beyond the funding period is questionable.

REVIEWER	Brown, Clare University of Arkansas for Medical Sciences
REVIEW RETURNED	14-Sep-2021

GENERAL COMMENTS	The proposed study aims to evaluate a program that offers fast-track referral services for four modifiable risk factors that are associated with adverse birth outcomes among pregnant women. While the study has multiple strengths, including targeting multiple modifiable factors, using a randomized trial, and evaluating multiple birth and implementation-related outcomes, the protocol would benefit from addressing the comments below. Major 1. A 30% reduction in low birthweight seems relatively high. The protocol would benefit from additional evidence that a 30% reduction can potentially be obtained. The introduction describes mixed evidence on the impact of addressing the modifiable factors, and provides only one study that found a large decline in adverse birth outcomes (Ricketts et al., 2005). While ANY decline is certainly important, the expected decline ultimately impacts the number of women needed to detect such a difference. Despite the substantial resources devoted towards reducing adverse birth outcomes, dozens of studies evaluating such programs indicate that such a large reduction may be unreasonable. 2. How will the researchers ensure that screening does not impact provision of care in the control group sites? The recruitment section indicates that data about risk factors will be collected by the health professionals who provide the prenatal care. It seems unlikely that a healthcare provider would feel ethically appropriate in disregarding a characteristics (e.g., interpersonal violence) that they are now knowledgeable about. While I recognize that the "standard of care" will be used once a risk factor is noted; it is possible that simply screening for such factors may increase awareness among providers in control clinics. 3. The authors are applauded for the clear outline of how each risk factor will be measured. 4. The proposed study sample size would be strengthened by indicating the estimated percent of infants that have their first follow up visit at the PHCU (i.e., when birth outcomes data will be collected). I am unfamiliar with the provision of care in such centers in Portugal, but in the US, women often go to a different clinic for prenatal care compared to the clinic used by the infant for pediatric care. Just a simple statistics indicating the percent of infants that may have this follow up would be helpful. 5. If I'm understanding correctly, the number of women needed for the study (2832) is estimated PRIOR to the exclusion of women that do not having any risk factors. Because less than 1/3 of the women had any of the risk factors in the pilot study, the number of participants likely needs to be much greater (and potentially a longer study time frame needed). 6. I would provide more clarity regarding how adherence will be measured (page 12, line 40) for women who have multiple risk factors and associated treatment/referral programs. 7. The pilot study noted particularly low rates of violence (1.4%) versus what was noted in the introduction (up to 22%). Were considerations made to change the survey questions to measure this risk factor? Minor 1. It is unclear what is meant by "having been born with low weight" on page 5 line 10. Does this mean having previously had a baby born low birthweight? 2. I would indicate that migrant women may be less likely to be included in the intervention given the study requirement to speak Portuguese. As this population makes up 10% of the births and may be more at risk, this may be an important limitation to note.

	3. On page 11 line 14, I would confirm that there are not other aspects that may end the study (e.g., miscarriage?).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. The authors described in the introduction section that the incidence of LBW is disproportionately higher among vulnerable communities such as migrants. However, due to language barriers a higher proportion of migrants would be excluded from the intervention. Meaning, the intervention effect (if there) would not be generalizable to vulnerable populations, the group who need the intervention most. I suggest looking for a mechanism to include them in the intervention.
Answer: Foreign women giving birth in Portugal account for approximately 13% of all births in Portugal (PORDATA, 2020. https://www.pordata.pt/DB/Portugal/Ambiente+de+Consulta/Tabela). We updated reference 12 in the introduction section for this more updated estimate. The majority of migrant pregnant women are from Portuguese-speaking countries (Lisi et al 2021, added as reference 62). Therefore, we do not expect the exclusion of large numbers of women due to language barriers. We have added this information in the discussion section.

2. Teenage pregnancy needs special care during pregnancy and delivery. What motivates the authors to consider mothers aged 14 to 18 along with those above 18? This age discrepancy could have an implication in the recruitment process and adherence to the intervention. Furthermore, what is the plan of informed consent for those aged 14 to 18 years?
Answer: In the last decades, teenage pregnancy has been decreasing in Portugal. In 2020, pregnancy in women aged 14 to 18 years represented around 1% of all live births. Considering the low rate of teenage pregnancy in the country and the review comments, we decided to modify the inclusion criteria for women over 18 years old. In the methods section, procedures subsection, we have removed the sentence “For pregnant women aged between 14 and 18 years old, an informed consent from the legal representative will also be signed”. We have also discussed the exclusion of teenage pregnancies in the discussion section.

3. Page 9, line 35-40: “The main hypothesis….”. The authors hypothesized that interventions targeting maternal psychosocial behavioral factors might reduce incidence of LBW. However, the planned intervention is referral. Referral does not mean the participants attended the consultation sessions. In addition, if the intervention is beyond referral, detailed intervention components should be described.
Answer: The intervention being tested is the fast-track referral. We´ve included a sentence in the methods section, procedures subsection, to make it clearer. This is a pragmatic clinical trial with minimal interference in the routine of health services. Therefore, women not attending the consultation sessions is a possibility (non-adherence to the intervention).

4. Study participants: including all women of any gestational age might not be a good idea. The intervention will have a different impact on the first, second and third trimester of pregnancy. Referral/consultation during late pregnancy won’t have or have less impact on low birthweight. How do the authors deal with this issue?
Answer: Most women in Portugal start prenatal care during the first trimester of pregnancy. Although the impact of the intervention on LBW is likely to be smaller, we decided to include women of any gestational age to assess wether there are differences. We will have information on gestational age at the time of inclusion and will be able to conduct sensitivity analysis to assess the effect of gestational age on the outcome LBW, if a large proportion of women will be included after the first trimester. We have added this information in the methods section, analysis subsection.

5. The sample size calculation is very clear. However, expecting a 30% reduction in LBW seems ambiguous. The study might not be sufficiently powered to detect a 10 or 20% decrease in incidence. I would recommend to consider a lower effect size in sample size calculation. I also suggest authors plan post-hoc power analysis.
Answer: We admitt that this is an ambitious goal but is in line with international goals to reduce low birthweight. Furthermore, the sample size to detect a 10 or 20% reduction was too large and not feasible. We´ve include the plan for conducting a post-hoc power analysis in the analysis subsection. We also added a sentence in the discussion section commenting on our primary outcome.

6. The authors described the intervention on page 15. Nevertheless, it is not clear whether the intervention is just 'referral' or there is a mechanism to check whether the participants attended the intended consultation. The intervention beyond referral needs to be described very well. How many sessions of consultation? How long? The intensity of consultation? What are the contents of the consultation for each risk factor? If the intervention is only referral, the primary outcome (incidence of LBW) is somewhat distant, which is less likely to have a 30% reduction.
Answer: The intervention is the fast-track referral. Pregnancy has a short duration, with a small window of opportunity for intervention in modifiable risk factors. Therefore, this study will verify whether shortening the period of referral to reference services that already exist in the Portuguese health system, under its usual operating conditions, can result in better perinatal outcomes. The care received after the fast-track referral will vary by service and will not be described as it is not part of the intervention. We have added this information in the methods section, intervention arm subsection, and in the discussion section, to make it clearer. We recognize that the 30% reduction in LBW is an ambitious goal. We have also included a comment on our primary outcome in the discussion section.

7. Who will be responsible for the fee and other procedures for the consultation? The participant/the research team?
Answer: There are no fees, as all reference services included in the study are public and free of charge. We included this information in the discussion section.

8. On page 15, the authors described the 'standard care' control group. The study will have multiple types of controls including consultation. How the authors will compare the effectiveness of the proposed intervention in comparison with multiple controls. Will they perform subgroup analysis?
Answer: Both intervention and control groups will have multiple types of consultation. This is a pragmatic clinical trial and the care provided is the current practice in the Portuguese health system. Our study aims to compare the effects of fast-track referral to reference services vs the standard of care, which may include several different approaches. We do not plan to perform subgroup analysis according to the type of care received in the control group.

9. Nutritional factors are important risk factors of LBW, however, they are not considered as part of the referral/intervention.
Answer: We recognize that there are several risk factors for LBW. In this study, we prioritized four modifiable factors according to the Portugal epidemiological context and nutritional factors were not included. We included this limitation in the discussion section.

10. Line 53-54: the authors mentioned that they will use the Edinburgh Postpartum Depression Scale to assess risk of depression. However, the cutoff for this scale varies for antenatal and postnatal period (Berking V. et al, 2011). Better to comment on it.
Answer: We would like to thank the reviewer´s comment but we were unable to find the study of Berking et al. The Edinburgh Postpartum Depression Scale has been validated for the Portuguese population, both in pregnancy and post-partum. Therefore, we adopted the cutoff that has been validated in the Portuguese population, according to levels of sensitivity and specificity, as well as detetion of both major and minor depressive syntoms in women (Reference 57: Areias ME, Kumar R,

Barros H, Figueiredo E. Comparative incidence of depression in women and men, during pregnancy and after childbirth. Validation of the Edinburgh Postnatal Depression Scale in Portuguese mothers. The British Journal of Psychiatry. 1996; 169(1):30-5).

11. Line 14-17: “The primary outcome (low birthweight) will be assessed during the first visit to the PHCU after birth”…When is the timing of first visit? The first visit might vary depending on the convenience of the women. The time should be specified clearly. Birthweight should be taken within 72 hours of delivery.
Answer: Our primary outcome is the birthweight measured in the maternity service immediately after birth. What we will assess in the first postnatal consultation is the information on birthweight, gestational age and type of delivery. We provided more details about the baby's appointment as requested by reviewer 2.

12. In page 14, line 54-57: the authors described that they will use multiple imputation if the missing is >5%. The handling of missing data depends on the pattern of missingness. MI only provides unbiased estimates under MAR assumption. Under MNAR assumption, MI won’t provide unbiased estimates and hence other advanced techniques might be required.
Answer: We rewrote the sentence to make it clear that the techniques that will be used to deal with missing values will depend on the pattern of missingness.

13. Do the authors consider subgroup analysis for teenagers? I suggest performing subgroup analysis based on age group as well as different control groups.
Answer: We have excluded teenagers. We do not plan to perform subgroup analysis based on different control groups as explained in item 8.

14. The discussion is written very well. I suggest commenting on planned activities to improve sustainability of the intervention effect beyond the intervention period. Sustainability remains the main challenge of public health interventions. The continuity of the intervention beyond the funding period is questionable.
Answer: We would like to thank the reviewer for this comment. Regarding the sustainability of the intervention, we believe that being a pragmatic study with the least intervention/modification on the routine healthcare, the intervention effect can continue beyond the study period. In fact, the study intends to use the care and resources already available to enable a better contact and to construct a more solid network that facilitates referral of women to the specific health care units. Also, the proposed intervention does not imply additional costs to the healthcare services. We added a small text about sustainability of the intervention in the discussion section.

Reviewer: 2
Dr. Clare Brown, University of Arkansas for Medical Sciences
Comments to the Author:
The proposed study aims to evaluate a program that offers fast-track referral services for four modifiable risk factors that are associated with adverse birth outcomes among pregnant women. While the study has multiple strengths, including targeting multiple modifiable factors, using a randomized trial, and evaluating multiple birth and implementation-related outcomes, the protocol would benefit from addressing the comments below.
Major
1. A 30% reduction in low birthweight seems relatively high. The protocol would benefit from additional evidence that a 30% reduction can potentially be obtained. The introduction describes mixed evidence on the impact of addressing the modifiable factors, and provides only one study that found a large decline in adverse birth outcomes (Ricketts et al., 2005). While ANY decline is certainly important, the expected decline ultimately impacts the number of women needed to detect such a difference. Despite the substantial resources devoted towards reducing adverse birth outcomes,

dozens of studies evaluating such programs indicate that such a large reduction may be unreasonable.
Answer: We admitt that this is an ambitious goal but is in line with international goals to reduce low birthweight. Furthermore, the sample size to detect a 10 or 20% reduction was too large and not feasible. Following reviewer 1´s suggestion, we´ve include the plan for conducting a post-hoc power analysis in the analysis subsection. We also added a sentence in the discussion section commenting on our primary outcome.

2. How will the researchers ensure that screening does not impact provision of care in the control group sites? The recruitment section indicates that data about risk factors will be collected by the health professionals who provide the prenatal care. It seems unlikely that a healthcare provider would feel ethically appropriate in disregarding a characteristics (e.g., interpersonal violence) that they are now knowledgeable about. While I recognize that the “standard of care” will be used once a risk factor is noted; it is possible that simply screening for such factors may increase awareness among providers in control clinics.
Answer: We would like to thank the reviewer for this comment. We corrected the “Standard of care” arm subsection by removing the word “screening”, as all women included in the study will have been previously screened for the four risk factors. We cannot guarantee that screening does not affect provision of care. However, the control group will have no access to the fast-track referral, that is, the intervention that we are testing. Therefore, we expect that the increase in detection is unlikely to affect the intended comparison. Raising awareness of these risk factors among providers in control clinics is actually a desired effect.

3. The authors are applauded for the clear outline of how each risk factor will be measured.
Answer: The authors thank the reviewer for the compliment.

4. The proposed study sample size would be strengthened by indicating the estimated percent of infants that have their first follow up visit at the PHCU (i.e., when birth outcomes data will be collected). I am unfamiliar with the provision of care in such centers in Portugal, but in the US, women often go to a different clinic for prenatal care compared to the clinic used by the infant for pediatric care. Just a simple statistics indicating the percent of infants that may have this follow up would be helpful.
Answer: In Portugal, the care for infants and adolescents is universal and free of charge at the national health system. Since 2016, all newborns in Portugal are assigned to a family doctor at the PHCU right after birth, usually the same PCHU where the woman was followed during prenatal care. The baby's first consultation takes place in the first week of life and the child is monitored throughout the first year of life free of charge. We added this information in the methods section, data collection subsection.

5. If I’m understanding correctly, the number of women needed for the study (2832) is estimated PRIOR to the exclusion of women that do not having any risk factors. Because less than 1/3 of the women had any of the risk factors in the pilot study, the number of participants likely needs to be much greater (and potentially a longer study time frame needed).
Answer: 2832 is the number of women with at least one of the four risk factors. We rewrote the sentence in the sample size subsection to make it clearer. In our sample size calculation we estimated that 20% of pregnant women would have at least one risk factor and would be eligible for our study. The prevalence of risk factor in the pilot study confirmed our previous estimates. Therefore, a longer study time frame will not be needed.

6. I would provide more clarity regarding how adherence will be measured (page 12, line 40) for women who have multiple risk factors and associated treatment/referral programs.

Answer: We have added a short paragraph providing more details regarding how we intend the measure adherence to the intervention.

7. The pilot study noted particularly low rates of violence (1.4%) versus what was noted in the introduction (up to 22%). Were considerations made to change the survey questions to measure this risk factor?
Answer: Prevalence rates of physical violence in Portugal ranged from 9.7% to 21.9%, depending on the study population and the type of instrument used. The study with the lower estimate of violence during pregnancy used the same instrument proposed in our study: the Abuse Assessment Screen. This scale is validated for the Portuguese population and is an easy and quick to apply instrument, being indicated to be used in the healthcare context. We think that the small sample size of the pilot study may have limited the detection of other cases of violence. Therefore, we have not made considerations to change the survey questions to measure this risk factor.

Minor
1. It is unclear what is meant by “having been born with low weight” on page 5 line 10. Does this mean having previously had a baby born low birthweight?
Answer: Thank you for the observation. He have rewritten the text to make it clearer that maternal birthweight is a risk fator for LBW.

2. I would indicate that migrant women may be less likely to be included in the intervention given the study requirement to speak Portuguese. As this population makes up 10% of the births and may be more at risk, this may be an important limitation to note.
Answer: Foreign women giving birth in Portugal account for approximately 13% of all births in Portugal (PORDATA, 2020. https://www.pordata.pt/DB/Portugal/Ambiente+de+Consulta/Tabela). We updated reference 12 in the introduction section for this more updated estimate. The majority of migrant pregnant women are from Portuguese-speaking countries (Lisi et al 2021, added as reference 62). Therefore, we do not expect the exclusion of large numbers of women due to language barriers. We have added this information in the discussion section.

3. On page 11 line 14, I would confirm that there are not other aspects that may end the study (e.g., miscarriage?).
Answer: We thank the reviewer for this comment. We included “miscarriage” and replaced abortion with “termination of pregnancy”.

VERSION 2 – REVIEW

REVIEWER	Brown, Clare University of Arkansas for Medical Sciences
REVIEW RETURNED	03-Dec-2021

GENERAL COMMENTS	The authors have addressed all concerns noted in my previous review.