Author’s response to reviews

Title: Calcium and vitamin D supplementation and/or periodontal therapy in the treatment of periodontitis among Brazilian pregnant women: protocol of a feasibility randomised controlled trial (THE IMPROVE TRIAL)

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Author’s response to reviews:

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BMC, Pilot and Feasibility Studies
Dear Editor-in-chief,

We are presenting for resubmission the revised manuscript entitled “Calcium and vitamin D supplementation and/or periodontal therapy in the treatment of periodontitis among Brazilian pregnant women: protocol of a feasibility randomised controlled trial (THE IMPROVE TRIAL)” for consideration for publication by the BMC: Pilot and Feasibility Studies (Ref: PAFS-D-18-00180).

We received the reviewers’ comments on the above paper and each point raised has been addressed by the authors. The changes are highlighted in the manuscript text. I hope that the changes made in response to the constructive comments and suggestions for improving the paper have made it acceptable for publication.

The results presented in this study have not been published, accepted, or submitted for publication elsewhere, nor does it duplicate already published material. The revised manuscript has been read and approved by all authors.

The authors declare no competing financial interests in relation to the work presented in the manuscript.

Yours sincerely,

Amanda R A Adegboye

We would like to thank the reviewers of our paper for the comments that helped improve our original manuscript. Here is a list of the changes we made according to the reviewers’ recommendations. Changes were highlighted in yellow in the manuscript.

Reviewer reports:

Reviewer #1: These are the comments related to the study that I have:

1. Will base-line measurements be taken before supplementing the patients with vitamin D?

We appreciate the reviewer comment. We included this information in the Methods/Design section and the Figure 1 was revised according to SPIRITS flow diagram.

The revised text states (Page 8, lines 207 to 210): “Baseline data is collected up to second trimester after checking for participant eligibility to the study (including dental screening for periodontitis) and prior to randomisation to intervention arms (T0); with follow up at third trimester (T1; during to the intervention trial) and 6-8 weeks postpartum (T2; after to the intervention trial).”
2. Pregnant patients with periodontal disease will be entered into the study. However there are two 'forms' of periodontal disease: chronic and aggressive. Patients suffering with aggressive periodontal disease may have a genetic association to the development of their disease. I therefore suggest that the researchers exclude patients with aggressive periodontitis.

Thanks for this comment.

To the best of our knowledge we did not include any women with aggressive periodontitis, as most of our eligible women presented mild chronic periodontitis. This could be due to the fact that women with aggressive periodontitis would be more likely to have poor overall oral health (presence of extensive caries) and therefore not eligible to the study.

Since aggressive periodontitis has a relatively low prevalence based on finding from two systematic reviews [1, 2], it is likely that we did not include women with this condition in our study. However, this chance cannot be completely ruled out as diagnosis of such condition in resource limited settings (such as public health clinics in low income areas in Rio de Janeiro, Brazil) might be complex. According the Susin et al. [1] a plethora of case definitions of aggressive periodontitis have been used over the last three decades. Demmer & Papapanou [2] also argue that there might be three essential diagnosis features however it is not always possible to easily identify these features:

• Rapid attachment loss and bone destruction

• Early onset: 1) Circum-pubertal onset constitute a key feature of Localized Aggressive Periodontitis, while 2) Generalized Aggressive Periodontitis is suggested to usually affect persons under 30 years of age, but patients may be older.

• Familial aggregation of the disease, “a feature that is oftenimpossible to ascertain upon examination of a patient, one quickly recognizes thatappropriate assignment of this particular diagnosis by the clinician – let alone by the epidemiologist- remains highly problematic”.


We included this information in the Discussion section as an additional limitation of the study (Page 19; Lines 568 to 573).

“However, this study has several potential limitations.

Since aggressive periodontitis has a relatively low prevalence based on finding from two systematic reviews [68, 69], it is unlikely that women with this condition will be recruited to the study. However, this chance cannot be completely ruled out as diagnosis of such condition in
resource limited settings (such as public health clinics in low income areas in Rio de Janeiro, Brazil) might be complex.”

3. I noticed that periodontal disease will only be diagnosed by periodontal charting. I don't think this is sufficient to confirm the diagnosis. What if the patient has pseudopockets with no bone loss. Therefore I think an x-ray (even bitewings) may be mandatory to confirm the diagnosis especially since there is an increase in gingivitis in pregnant patients.

Thank you for the comment.

Although the American College of Radiology states that no single diagnostic x-ray has a radiation dose significant enough to cause adverse effects in a developing embryo or fetus and that the ADA [3]; ACOG [4] and Maryland Department of Health [5] also state that having dental X-rays during pregnancy is considered safe we did not have ethical approval to conduct such procedure. During our consultation with the GPs and obstetricians in the clinics prior to the data collection it was clear that they did not approve such practice. We found out that most clinicians (including the dentists) had a conservative approach toward their practice.

Other studies involving pregnant women also did not use the X-rays to periodontritis diagnosis [6; 7; 8]


We included this information in the Discussion section as additional study limitation (Page 19; Lines 574 to 577).

“Although having dental X-rays during pregnancy might be considered safe [70, 71] we did not have ethical approval to conduct such procedure. However, similar to previous studies on periodontitis status among pregnant women, an X-ray was not taken to help confirm the diagnosis [72, 73, 74].”

Reviewer #2: Thank you for submitting this interesting trial protocol. I have a number of suggestions for improving the flow and structure of the protocol:

1) The authors should offer some benchmark or threshold levels for each feasibility outcome, which in turn would inform the authors/reader if a future study is indeed feasible (for example, what does "acceptability" mean in practical terms for the feasibility outcome? And what % threshold would be required to determine acceptable recruitment, adherence and retention?)

Thank you for the comment. We made the appropriate correction.

The revised text states (Page 14, lines 407-411): “To evaluate the reliability and completeness of outcome will be considered a feasibility threshold of 70-75% for recruitment. Furthermore, in this study will be considered an adherence rate of 70% and a loss to follow-up between 20-30%. Adequate acceptance of the study design and intervention will be based on qualitative data on barriers and facilitators to the intervention and taste test, number of sachets consumed and feedback from the follow up phone calls”

2) Analysis of pilot studies should focus on confidence interval estimation rather than hypothesis testing, as pilot studies are not powered to determine treatment effects with any confidence. Therefore, all inferential statistics should be treated with caution. I would suggest that the authors rewrite the statistical analysis section, stating that analysis will focus on confidence interval estimation, and that all hypothesis testing/regression modelling will be viewed as entirely exploratory. Useful references relating to this issue include:


This is a very good point. We appreciate the reviewer’s comment and revised the statistical analysis section to make this point clearer.

The revised text states (Page 15, lines 447-450): “It is important to highlight that the present study is a feasibility trial. Thus, the priority will be performance of descriptive analysis and estimation of sample size for the main study and that the statistical analysis related to results from hypothesis should be interpreted with caution [9] and viewed as entirely exploratory.”