Author’s response to reviews

Title: A randomized controlled trial to assess the clinical and cost effectiveness of a nurse-led Antenatal Asthma Management Service in South Australia (AAMS study)

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Author’s response to reviews: see over
Dear Editor

We thank the reviewers for their informative and thorough feedback and for the opportunity to revise the manuscript in accordance with their suggestions.

We value the opportunity to further improve this manuscript with the following changes outlined below.

**Major concerns:**

1. **Randomization is not explained in detail. Stratified randomization is described variably as by disease severity in the abstract, severity and parity in the manuscript, and no mention of how the two sites are randomized is included.**

   The randomisation process has been clarified in the abstracts:

   Eligible women with asthma, stratified by treatment site, disease severity and parity, will be randomized into one of two study groups: either the ‘Standard Care Group’ or the ‘Intervention Group’

   Treatment site is included as an additional stratification variable. That is randomisation is undertaken within each treatment site. This has been amended in the manuscript:

   “After the baseline assessment of asthma at 18 weeks gestation, women will be randomised to receive either standard care or nurse-led asthma management during pregnancy by contacting the central telephone randomization service at the University of Adelaide. The telephone randomization service will use a randomization schedule with balanced variable blocks, prepared by an investigator not involved with recruitment or clinical care. Stratification will be undertaken according to treatment site, parity and asthma severity. During the randomization call, eligibility will be checked and information collected to enable stratification and to assist in follow-up.”

2. **The study design validity may be compromised by two factors: 1. Conducting the study at 2 very different sites, and 2: the lack of an attention control strategy for the control group. These two issues should be dealt with before the trial begins. There is no mention of how the two sites may differ in implementation of the intervention or how**
this potential difference will be assessed, managed, and included in the statistical analysis.

We acknowledge the challenges associated with conducting the study across two different treatment sites. The sample size was derived from an expectation that there will be some differences between the 2 sites such as the potential for treatment differences and observed effect size due to differences in existing levels of care and/or participant characteristics (eg: SES). For example, one hospital has on-site respiratory specialist services while the other has a part-time visiting respiratory specialist service. There are also significant socioeconomic differences across the sites. These differences may influence the implementation and successfulness of the intervention across both sites.

We have included an additional sentence to clarify this:

“In recognition of potential differences in the implementation and successfulness of the intervention across two distinct treatment sites, the sample size was calculated to ensure adequate statistical power within each treatment site.”

The issue of controlling for the large amount of time and attention to be received by the Intervention group with no plan for the control group will create the potential of an alternative explanation for the results.

We do not believe that this is a source of bias. The provision of a new asthma management service is expected to take additional time, as it consists of a 45 minute consultation and 15 minutes for data collection. The control group have the same number of visits, with each taking 15 minutes for data collection. Unless women were provided a sham asthma management service in the control arm then there would be no way in which to ensure both groups have the same time commitment.

Minor concerns:
1. Abstract: Under trial entry and randomization you specify the sample will be stratified by disease severity only. In the body of the paper you say stratification is by disease severity AND parity. Please reconcile these sentences so they say the same thing.
This has been corrected.

2. Pg 6 Asthma exacerbations during pregnancy are associated with adverse outcomes: Para 1, Line 2: The definition of an asthma exacerbation as you give it here needs a reference. Please add. Most definitions do not include peak flow rate, exclude or reference.

This was a mistake, peak flow should not be included in this definition.

“The definition of an asthma exacerbation is any asthma related event that involved one or more of the following; a hospital admission, an unscheduled doctor visit, a course of oral steroids or an increase in medication use.”

3. Pg 7 Section: Risk factors for exacerbations. Para 1, Line 1-3. The reference cited is for one study of 146 women which does not warrant the statement that exacerbations are most likely between 17 – 34 weeks gestation…..unless these findings were confirmed in other studies. Revise to specify the findings are from one study only – generalizability is not yet been shown.

We have amended the sentence to make it clear that this statement is based on evidence from a prospective cohort study of women with asthma.

“While exacerbations can occur at any time during pregnancy, evidence from a prospective cohort of women with asthma identified that exacerbations were most likely in the second and third trimesters between weeks 17 and 34, with a peak incidence around 25 weeks gestation[10].”

4. Pg 8 section: Existing evidence ….paragraph 1, lines 1-5. What groups are being compared in this nonrandomized study to determine a significant increase in birth weight? Compared to who?

Sentence has been adjusted

5. Pg 9 paragraph 1, line one: Please clarify the statement that FeNO was associated with a significant reduction in exacerbations rate: was it the FeNO that was associated
or was it the increased use of inhaled corticosteroid? If the latter, then insert the words “to titrate the dose of inhaled corticosteroid” after “FeNO in line 1.

FeNO is used to adjust asthma treatment (i.e. increase or decrease inhaled corticosteroid therapy). We have clarified this in the manuscript:

“Use of FeNO to adjust asthma treatment was associated with a significant reduction in the exacerbation rate during pregnancy (0.288 vs. 0.615; p=0.001) and a reduction in neonatal hospitalizations (8% vs. 17%; p=0.046) [28].”

6. Pg 11 Recruitment. Paragraph 1, Line 5: “ventolin or a preventer” Why did you use a brand name for the inhaled beta2 agonist and a colloquial word for the control medication? Was it reliever and preventer? Is the “preventer” assumed to be an inhaled corticosteroid? There are other types of “preventer” asthma medications, such as leukotriene modifiers.

The use of Ventolin was a mistake, this should have read salbutamol. We have corrected this in the manuscript:

“As well as “Have you used any asthma medications in the last year such as salbutamol or a preventer?””

7. Pg 12, paragraph 1, line 12. What is meant by “a purpose designed Asthma Knowledge Quesstionnaire”? Did you create it for this study, and is it not validated? Explain.

The asthma knowledge questionnaire is used to assess women’s basic asthma knowledge as well as their knowledge of specific issues unique to asthma management in pregnancy. The asthma knowledge questionnaire has been validated as part of our previous prospective asthma study and has not yet been published.

8. Pg 12, Paragraph 3: Randomization. Randomization and stratified randomization methods need to be described in detail so that replication is possible. What about the
randomization at 2 sites? How does a “telephone randomization service” work? What are number of blocks and how are they filled?

The telephone randomisation service involves a specially designed automated algorithm, which tailors the stratification requirements and blocking required for a particular trial. Recruiters respond to each part of the algorithm which then builds and balances the randomisation in real time and then advises the recruiter of the group allocation.

“Thereafter the baseline assessment of asthma at 18 weeks gestation, women will be randomised to receive either standard care or nurse-led asthma management during pregnancy by contacting the central telephone randomization service at the University of Adelaide. The telephone randomization service will use a randomization schedule with balanced variable blocks, prepared by an investigator not involved with recruitment or clinical care. Stratification will be undertaken according to treatment site, parity and asthma severity. During the randomization call, eligibility will be checked and information collected to enable stratification and to assist in follow-up.”

9. Pg 12 Paragraph 4: Standard Care Groups: What exactly happens to women who are randomized to this control group: If you want to just reference Practice Guidelines, you need to reference it so that your method of standard care can be replicated. If some women are being managed by respiratory specialists in the control group, how will you control for contamination? Is this plan meant to follow the intention-to-treat principle? Do you plan to identify and code these women differently for posthoc analyses?

The South Australian Perinatal Practice Guidelines are available online, available from [www.sahealth.sa.gov.au](http://www.sahealth.sa.gov.au). We have included this link in the manuscript to enable people to locate it.

To protect the integrity of the randomisation procedure it is necessary to follow the intention-to-treat principle. This involves women being analysed as belonging to the group they were randomised to, regardless of the level of care they actually received. There are a number of women who will go out and seek additional support for managing their asthma, or women that are already seeing a respiratory specialist or general practitioner on a regular basis to
help manage their asthma. This reflects standard care in that it is reliant on women self-managing their asthma during pregnancy.

A separate post-hoc analysis will be undertaken to evaluate potential differences in care received by women in the standard care group. We will be collecting varying measures of treatment intensity (i.e. visits to general practitioner, respiratory specialist or respiratory nurse in the community setting) which will enable us to compare outcomes according to these additional factors.

10. Pg 13, paragraph 2, lines 1-4. Intervention Group: Explain how the asthma action plan is “individualized” from the standard template? What variables or patient characteristics are used to “individualize”?

The asthma action plan is individualised because not every patient’s asthma management strategy is the same. Some women will be on different relievers (i.e. salbutamol Vs. terbutaline) or different preventers (some of which they can also use as a reliever [i.e. Symbicort]). Not all women will require the use of a spacer with their preventer medication, depending on the form (i.e. MDI, accuhaler, turbuhaler). Lastly, asthma triggers will differ and the use of peak flow measurements to detect a worsening of asthma control must be tailored to the individuals baseline peak flow measurements.

How much time is spent by the respiratory nurse with the participants in the Intervention Group?

The asthma education visit takes approximately 45 minutes to complete.

How will you control for all this attention in the Control group?

There is no need to control for this extra attention as the intervention being measured is the use of an asthma education service conducted by a respiratory nurse. To adjust for additional time spent in the asthma education session would be to adjust away the potential benefit offered by educating women about their asthma and providing them with an asthma action plan.
11. Pg 14: Data Collection: at the data collectors blind to study assignment?

Blinding the outcome measures is impractical as these form a critical component of the delivery of the asthma management service (i.e. assessment of asthma control). Furthermore, key outcomes are objective (i.e. asthma exacerbations) so the risk of bias from the assessor is minimal. Outcomes will be further validated through additional data sources including doctors, hospital and pharmacy records to validate recording of asthma exacerbations as measured by an unscheduled doctor visit, admission to ED or hospital or use of oral corticosteroids.

Will you have evidence of parity between providers in their level of skill at performing spirometry?

All research nurses will complete an accredited spirometry course with Asthma Australia and consistency in technique will be part of the quality assurance assessment every 6 months.

Will the same amount of time be spent at the data collection visits in both groups?

The same amount of time is spent in both groups on data collection. The only time difference is that women in the intervention have a 45 minute asthma education visit, on top of the estimated 15 minutes for data collection required at each visit.

Consider spending the same amount of time with participants in both groups by using a different control strategy in the Standard Care group rather than leaving it up to chance. At the least, participants in the Standard Care Group should be seen at 18 weeks same as the Intervention Group – attention control.

As outline on the study flow diagram, all study participants are seen at 18 weeks for a baseline asthma assessment and data collection. Women randomised to standard care go home after the data collection is complete. Women randomised to the intervention have a 45 asthma education visit to discuss management strategies, techniques and develop an individualised asthma action plan.

12. Pg 15: Primary study outcomes: Clarify that the outcome of incidence of asthma exacerbation is compared between groups, that is you hypothesis is there will be an
absolute risk reduction of 20% in the intervention group compared to the control
group. This end point is not clear as stated.

This has been amended:

“Based on previous research undertaken by our research group it is hypothesised that
participation in the Antenatal Asthma Management Service will result in a 20% reduction
(absolute) in the incidence of asthma exacerbations during pregnancy in the intervention
group compared to the control group [28].”

13. Pg 16: Sample size: lines 1-3. Isn’t the primary outcome is difference between
groups in exacerbation rates, not “change” in exacerbation rate. In this new RCT you
are not comparing the reduction rate to the literature (45%). The comparison is
between the 2 study groups, so from your hypothesis you are expecting an absolute
difference of 20% less exacerbations in the intervention group vs the control. Is this
what you mean to say? Also, in the last sentence of this same paragraph you allude to
the power to assess the other important outcomes. Were power calculations done for
these other outcomes? If so it should be reported for each secondary outcome variable
that you plan to analyze. If not, then you cannot make this statement in the last
sentence.

We have amended the sentence to state “difference” in exacerbation rate:

“The sample size of 378 pregnant women at baseline (189 in each group) was determined by
power calculations (using 90% power and a 5% level of significance) using the primary
outcomes of difference in exacerbation rate between treatment groups.”

The sample size is derived from evidence available from the literature on the expected exacerbation
rate and the determined achievable reduction. Existing literature outlines an expected rate of 45% and
we aim to reduce this by 20% to 25%. The exacerbation rate in the study will be compared between
the intervention and control groups.

We have removed the final sentence of the paragraph as we are not reporting the sample size
calculations for these additional outcomes.
14. Pg 16, paragraph 1 Statistical Analysis: What “adjusted” analyses are planned?
Adjusted for what? In this paragraph the difference in exacerbation rates is clearly the primary outcome. Use the same language in the previous sections.

The term adjusted analyses was an error, given women will be randomised at study entry there will be no need to adjust for baseline characteristics. This has been fixed in the manuscript.

15. Pg 16, paragraph 2 lines 6-10. Are these “planned sub-analyses” the same as the adjusted analysis in paragraph 1. Clarify by making lines 6-10 a separate paragraph since these analyses sound like you plan to do this analysis on the primary outcome as well as the secondary ones.

New paragraphs have been inserted

Consider using STATA if SPSS is inadequate for the mixed effects models and comparisons you want to make.

We will consider using Stata if SPSS is not adequate for the mixed effects models.

16. Pg 17: Cost Effectiveness. A general plan for collecting the data needed to determine costs is described. But it is not clear what statistical approach will be used to determine cost effectiveness of the Antenatal Asthma Management Service intervention. This will be an important outcome of the study as it will affect the generalizability of this intervention.

The cost-effectiveness section has been redrafted to describe methods for imputing missing cost data, for adjusting for any imbalances in baseline characteristics, and for representing uncertainty around the mean estimates of cost-effectiveness.

17. Pg 18 Trial Management: It is not clear whether the data monitoring committee includes the adverse events committee or is separate from the data monitoring committee. All adverse events should be reviewed not just deaths.
What do the abbreviations CI and AI mean? Spell out.
An independent data monitoring committee will be established, with terms of reference jointly defined between trial investigators and the independent committee members prior to study commencement. A separate multidisciplinary adverse events committee blinded to treatment allocation will review adverse events including maternal hospital admissions, maternal death, stillbirth, miscarriage, and infant deaths. These data will be made available to the independent data monitoring committee.”

CI and AI have been replaced with:

“study investigators”

18. What is included in the “quality assurance review” conducted by the respiratory specialist every 6 months? What are the credentials of this specialist?

The respiratory specialist is a respiratory physician who has over 30 years experience working as a senior respiratory consultant across a range of settings. We have clarified this in the manuscript:

“A respiratory physician who specialises in asthma management will provide a quality assurance review of the asthma management clinic every 6 months at both sites to determine that nurse-led asthma education and management practice is consistent between sites and practice standards are maintained.”

We hope that you find these changes satisfactory and look forward to a favourable response.

Yours sincerely

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