Author's response to reviews

Title: The Be Our Ally Beat Smoking (BOABS) study, a randomised controlled trial of an intensive smoking cessation intervention in a remote Aboriginal Australian health care setting

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The Editor
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Dear Editor

RE: MS: 4095712510304580 The Be Our Ally Beat Smoking (BOABS) study, a randomised controlled trial of an intensive smoking cessation intervention in a remote Aboriginal Australian health care setting

Thank you for the opportunity to respond to your, as well as the reviewers suggestions regarding this manuscript. We have taken these comments into account and have revised our manuscript.

Below are our responses to the editor's and reviewers' comments.

Editor:

I would like to congratulate the authors for conducting an intervention trial in a very difficult and under-researched area of Indigenous health. Nevertheless, there are some issues with the manuscript that need to be carefully considered. I agree with the reviewers' comments and have added some of my own below, that would need to be addressed before the manuscript is considered further. I strongly urge the authors to consider being more direct in accepting that the results of their trial are essentially negative (that is, the results, discussion and interpretation should more clearly state the negative result rather than use phrases such as "...while the proportion remained higher in the intervention group, it was no longer statistically significant."). That clear an unequivocal interpretation would strengthen, rather than detract from the manuscript.

We acknowledge the study was underpowered due to difficulty with recruitment and agree we need to avoid implying that on its own that the BOABS study has a positive result. We have therefore adjusted the language in the paper accordingly:

However, based on a combination of self-report and cotinine level at final follow-up, the final results (2.4; 95% CI, 0.8-7.4, P = 0.131) were not statistically significant. (p12)

The current study did not demonstrate a statistically significant benefit from the BOABS intervention and due to difficulties recruiting participants did not have the power to do so. (p13)

The study was negative in the sense that it did not demonstrate a statistically significant effect, however that is not the same as saying the result supports ‘no association’ or provides evidence against an association and we also need to avoid implying this as well. The estimated effect size was over 2 and this, if substantiated, is a clinically important effect. This was not statistically significant, hence not proven. We agree that it would be
inappropriate to draw strong positive conclusions, but it would also not be appropriate to draw the conclusion there is no effect when a positive effect is more likely than not.

1. Please explain why you used a 2:1 allocation ratio

The planned intervention was very labour intensive and hence we decided that a 2:1 ratio would be a worthwhile approach to increase power without substantially increasing workload. While recognising some of the challenges of recruitment we underestimated the difficulties of recruitment and in hindsight it would have been better to have used a 1:1 ratio. We have added “As the planned intervention was labour intensive” to the beginning of the sentence Participants were allocated to usual care or intervention groups in a 2:1 ratio (p6).

2. Please identify the strategies put in place to avoid contamination between the intervention and treatment as usual groups. It's not sufficient to say "Considerable effort went into preventing contamination..." (page 12).

This has been modified to: There was repeated clinic and research staff training about roles and responsibilities to minimise contamination between groups.

3. Is there any measure of the extent of exposure to the intervention for those allocated to the intervention group - it's an important issue because the lack of effect may be due to a lack of exposure to the intervention.

We have included the following (p 11):

An average of 7 of the 12 planned formal smoking cessation sessions were provided by the Aboriginal researchers to participants in the intervention group. Additional informal contact occurred throughout the study period (eg Aboriginal researchers meeting participants while out in the community and stopping to discuss how they are going with their quit smoking attempt). Twenty two (40%) participants in the intervention group had documented action plans. In addition to the content delivered by Aboriginal researchers during smoking cessation counselling sessions (see methods), they also provided service mapping and linkages to other services. Individual case conferences with clinic staff did not happen as frequently as planned and only occurred as required. Few participants attended group sessions.

4. What's the definition of "low urinary cotinine" (page 7)? Why use low instead of zero?

The definition of low urinary cotinine (<50ng/mL) was listed further down on p7 (now p8). Cotinine can be present due to passive smoking (see reference 14). We selected a cut-off that would best distinguish between passive and active smoking (see reference 15).

5. The methods state multiple questions were used to assess self-reported quitting. Please specify which questions (it's an important issue for replication) and whether the questions used have any evidence for their reliability and validity.

We have added in the specific questions asked: Are you still a smoker? Have you smoked since the last BOABS Smoking Checkup? When was your last cigarette? On an average day how many cigarettes a day do you smoke?

When we designed the protocol there was no evidence of the reliability or validity of these questions, which is why we validated smoking cessation using urinary cotinine. Subsequent studies suggest that self-report alone may not always be valid (see reference 21).

6. Given there was a significant difference in age between groups, why was this difference not controlled for in the statistical analysis? Similarly, what is the basis for saying the age difference is not clinically meaningful - my guess is that smoking cessation would likely increase with age anyway, so how much of the intervention effect is a consequence of an older average age ain the intervention group?
Age was tested in the logistic regression model and was not associated with quitting. We tried models that included age in age groups and also models with age as a linear variable. We have added Age to the sentence Gender was not associated with quitting (p13).

7. Please state why data were not analysed on an intention to treat basis
The data were analysed on intention to treat basis (see Table 3). As per the recommendation from reviewer 2 we have moved the information from the footnote into the table. It is a CONSORT requirement to use the term “based on the study arm to which participants were originally assigned” rather than “intention to treat”.

8. On page 10, I found the middle paragraph a bit confusing (and I think follow up at 6 months is 58% not 60%) and also the first 3 sentences of the next paragraph. For example, the middle paragraph seems to say 7 quit smoking in the usual care group and 3 in the intervention group, which is different to 13 in the next paragraph and different again to the numbers in Table 3. Please clarify.
Table 3 only refers to 12 month follow-up. We have clarified the section on the 6 month follow-up and moved it to the end of the results section as per the recommendation of Reviewer 1: Follow-up at six months was only 59% (Figure 1) with seven of the 64 (11%) and three of the 33 (9%) participants in the usual care and intervention groups self-reporting quitting smoking at six months. This was not validated with urinary cotinine.

We have clarified the section on the final follow-up: One hundred and forty-four (88%) participants were followed-up after 12 months, with 92 (56%) providing urine samples for validation of smoking cessation. Loss to follow-up was due to participants moving home and Aboriginal researchers not knowing where they moved to so they were unable to contact them.

We have changed the final paragraph on this to read:
For four participants there was a discrepancy between self-report smoking status and cotinine levels. Thirteen participants reported quitting smoking and 13 had a cotinine level consistent with not smoking. Two smokers (usual care group) claimed they had quit smoking at the final follow-up, however both reported quitting within the last 24 hours and had high cotinine levels. Two participants (intervention group) who self-reported continuing smoking had cotinine levels consistent with not smoking (below the level of detection of 20 ng/mL). One of these participants had the urine sample collected three months after the final questionnaire was administered and reported not smoking at the time of urine collection, no reason was identified for the other discrepancy as the participant was clear she was still smoking. As participants were only classified as not smoking if they satisfied both criteria, these four participants were classified as still smoking at final follow-up.

Reviewer 1:

1. P.7 Procedures. Compared to Protocol paper have dropped mention of weekly case conference with GP, and service mapping and linkages. Why? The authors should add a new section in the Results and describe what elements of the program were delivered, eg how many visits were completed, pharmacotherapy used, etc. Can shift the final comment in para that few attended monthly groups to there. This is essential for readers to know what has been done. Similarly it would be useful to know what services were provided to the ‘usual care’ group. This is particularly important given the final two sentences of the Conclusion.
We included information about service mapping and linkages on P7: The content delivered by Aboriginal researchers … case management to address these by linking participants with additional non-health support agencies (e.g. public housing, welfare, domestic violence and alcohol services)…
We have added the following to the results section (p11):

“An average of 7 of the 12 planned formal smoking cessation sessions were provided by the Aboriginal researchers to participants in the intervention group. Additional informal contact occurred throughout the study period (e.g., Aboriginal researchers meeting participants while out in the community and stopping to discuss how they are going with their quit smoking attempt). Twenty two (40%) participants in the intervention group had documented action plans. In addition to the content delivered by Aboriginal researchers during smoking cessation counselling sessions (see methods), they also provided service mapping and linkages to other services. Individual case conferences with clinic staff did not happen as frequently as planned and only occurred as required. Few participants attended group sessions.

Clinic staff were reported to have provided the same level of routine care relating to smoking cessation to both groups: 23% of participants reported that they spoke to clinic staff about smoking during the study. Overall participants reported that clinic staff provided advice on risks of smoking (75%), recommended quitting smoking (71%), recommended medication to assist with quitting (54%), discussed passive smoking (61%), provided practical advice on quitting (50%), provided written advice on quitting (46%), arranged for a follow-up appointment (46%), and set a quit date (32%). There was no difference between groups. Participants were predominantly offered NRT Patches (39%) or varenicline (14%).”

We have changed the second last sentence of the conclusion to:

Taking into account the feasibility and cost-effectiveness of RCTs and cluster randomised trials, the priority should be to demonstrate the effectiveness of programs based on personal support to quit smoking in a real world setting.

2. P.10 Results. Please provide more information about the 70 excluded as not meeting inclusion criteria, and pls discuss in Discussion the implication of these exclusions and those unable/unwilling to consent (may need to unpack this category in results too – I assume most just unwilling) for generalisability of results.

We have broken down the unable / unwilling to consent in Figure 1 and added the following to the results: People were unwilling to consent because they did not want to take part in a research project or were not interested in quitting smoking.

In the discussion we have added: In this study there were a number of reasons why people chose not to enrol even though they wanted assistance to help quit smoking and most of these related to the consent and/or the randomisation processes. Therefore, we believe that more people will be interested in joining a program than a research study. It is unclear whether the people who did not want to participate in research would be more or less likely to quit than those who did participate. (p 14)

3. P.11. results. Fourth para. Please describe what results were found with no imputation.

We have removed the imputation from Table 4. As we did not have complete follow-up for nicotine dependency, we have added in the proportion with nicotine dependency ≤5 at baseline who had a nicotine dependency score recorded at final follow-up. Changes from baseline to final follow-up of nicotine dependency score ≤5 (decreased dependency, no change, increased dependency) were compared using the Cochran-Mantel-Haenzel test for linear association. This has been added to the methods (p 9).

4. P.11. results. Please include a summary of the process evaluation indicators – as described in the Protocol paper.

This is now included in the results section (e.g., number of sessions that occurred) (p11).

5. P.11. Results. The secondary ‘cut down’ measures in Protocol paper have
been replaced with a quit attempt outcome. Please explain why, or include as per Protocol.

We did not include the proportion of participants who reported 20% or greater reduction in the number of cigarettes smoked each week, as it has been argued elsewhere that reducing daily cigarette intake is of limited preventative value. There was no difference in the proportion of participants who reduced the number of cigarettes smoked daily by 20% (usual care: 51.4%, 95% CI 39.4-63.1%; intervention: 42.9%, 95% CI 26.3-60.6%, p = 0.407).

We have added information on this into Table 4.

6. P.12. Discussion. First para. There is no stat sig difference in the combined results and the non-Indigenous results, please adjust text accordingly. These results are consistent with the non-Indigenous results.

We have clarified this. We have changed “compares favourably with” to “is similar to”.

It seems worthwhile here to make some comment on the intensity of the interventions (and controls) in BOABS and Eades and in the compared non-Indigenous trials. They spend much time talking about the ACCHS setting and Aboriginal involvement in the intervention. But it seems to me that the high intensity of the intervention (therefore need more on process measures) and the high prevalence of smoking in this population are also important.

We have added the following to the discussion (p14):
Both studies while more intensive than usual care were less intensive than originally planned. The participants in the BOABS intervention group received an average of seven of 12 smoking cessation sessions over 12 months and 40% had documented action plans for helping them to quit smoking. In contrast only 23% of participants in the usual care group reported discussing smoking cessation with clinic staff. In the non-Indigenous setting a systematic review of physician advice found increasing the intensity of the intervention showed a small advantage over minimal advice (RR 1.37; 95% CI 1.2-1.6) [26]. The level of intensity in these studies varied from brief intervention to repeated advice to quit as an inpatient with follow up in a special clinic.

Increasing the intensity of the intervention may have had an impact on the quit rate in the intervention groups of both the Eades study and BOABS. Although the Australian Indigenous smoking prevalence is high, there was only a 3% quit rate in a local program delivered at one of the sites prior to the BOABS intervention (personal communication CN). The quality of the relationships between the BOABS Aboriginal researchers and participants may well have had an impact. A qualitative evaluation of the observations and notes from the BOABS Study is required to further elucidate this.

Minor Essential Revisions
1. Background. P.3. The estimates of smoking prevalence used should be tightened. The most recent reliable figures for Indigenous Australians are from the 2008 NATSISS and for non-Indigenous or all Australians from 2010 (not 2007 as cited) NDSHS or the 2011 AHS. They should also specify age group included (14+,15+, 18+) and whether for current or daily smoking, as these criteria vary between reports.

We have changed the first sentence to: In 2008, the age-standardised prevalence of current smoking among Indigenous people was more than double that among other Australians (49.8% compared with 20.5% of those aged 18 years and over) [1].

2. In the same para, ‘much of the health disparity’ is inappropriately imprecise when there are precise estimates available in the literature. Please include these and reference to the work by Vos et al.

We have added in the following to the introduction:
Ischaemic heart disease and type 2 diabetes contributes 14% and 12%, respectively, to the Indigenous health gap [3]. Indigenous men and women 35 – 54 years of age die from
ischaemic heart disease at 7.2 and 16.6 times, respectively, the rate in the non-Indigenous Australian population [4]. In addition similarly aged Indigenous men and women die from chronic lung disease at a rate 9.7 and 13.9 times greater respectively, and from lung cancer at a rate twice that of non-Indigenous Australians [4]. Smoking substantially increases the risk of both macrovascular and microvascular complications of diabetes and may have a role in the development of type 2 diabetes [5].

3. Background second para first sentence. This is a contested view in the tobacco control literature, and needs to be toned down to reflect this. Many in tobacco control emphasise most quitting occurs ‘unassisted’ (so it is not necessarily notoriously difficult for them), with only a modest additional benefit shown by these trials. Others emphasise the utility of this additional benefit. We have changed this sentence to: While many smokers quit unassisted, for others helping them to become and remain non-smokers is difficult.

4. P.4 First para, second sentence. This ‘less likely to stop’ sentence is a bit vague. Please provide more detail on the Indigenous/non-Indigenous comparisons of quit attempts and successful cessation on which this is based. Or drop sentence. We have dropped this sentence.

5. P.8. Statistical methods. Please include the criteria was used for dropping variables from regression model.
We have removed the logistic regression based on the recommendation of Reviewer 2 and given this did not provide additional understanding regarding the impact of the intervention on the primary endpoint. Detail regarding the regression model is therefore not required in the methods and has been modified to “Multivariate analyses did not significantly change the results and hence have not been included”.

The protocol paper stated “Two forms of regression analysis will be considered for the primary outcome - logistic and Cox proportional hazard”. Given the limited time based information we decided Cox proportional hazard analysis was not appropriate. We explored logistic regression analyses and the outcome results were similar to the contingency table analyses using \( \chi^2 \) tests.

7. P.8. Statistical methods. Please explain why a different imputation method used than in Protocol paper
We assume the reviewer is referring to the imputation method referred to in point 3 (Major revisions). As previously mentioned the different imputation method has been dropped and we have included both baseline and final follow-up nicotine dependency for participants who had both recorded. This is now included in the methods.

8. P8. This meta-analysis is a justifiable addition, but it is not in the Protocol paper, and this should be made clear. It is probably reasonable to include only the other published Australian Aboriginal tobacco control RCT. But the description of the selection criteria is imprecise. This study does include pharmacological interventions (and non-pharmacological support). There are a couple of Quitline and text messaging RCTs from NZ which included significant numbers of Maori that it may be reasonable to include on current criteria, or the wording should be tightened.
We have tightened the wording on the inclusion and exclusion criteria for the meta-analysis and added that it was not part of the study protocol (p9):

Based on CONSORT recommendations of placing the results of this study into context [17] we carried out, post hoc, an associated systematic review of smoking cessation trials in Indigenous populations. Our selection criteria for inclusion in the meta-analysis were
randomised controlled trials of interventions with validated smoking cessation in Indigenous populations. Our exclusion criteria were 1) trials comparing pharmaceutical interventions or pharmaceutical intervention compared with placebo and 2) all studies where quitting smoking was not biochemically validated for all participants who self-reported they had quit smoking (e.g., urinary cotinine). A recent meta-analysis of four studies reported a RR of 1.43 (95% CI: 1.03–1.98) for smoking abstinence at 6–12 month follow-up in the intervention group, based on a very low quality of evidence [6]. Additional searches of the Cochrane Tobacco Addiction Group Specialised Register of Trials (June 2013), MEDLINE (June 2013), online clinical trial databases and publication references for potential studies were also conducted. The four trials reported in the recent review did not meet the selection criteria: two were not randomised [18, 19], one assessed the efficacy of a pharmaceutical intervention (bupropion) compared with placebo [20], and one had smoking cessation validated in only a subset of participants who self-reported that they had quit smoking [21].

This meta-analysis was not part of the original study protocol. (p10)

9. P10. Suggest move secondary outcome data on 6 month outcomes to section discussing secondary outcomes, and start with primary outcome data results.

Moved as suggested.


Removed as suggested.

11. P.11. Third para. Please list all variables in final model. And replace ‘favorably influenced’ with the more accurate’ were associated with’.

Changed as suggested.

12. P.13. third para, first sentence. Please re-write this sentence as BOABS is a clinical outreach intervention for individuals not a public health intervention.

We have added in: Similarly RCTs may not be the best design for complex clinical individualised interventions such as BOABS.

Reviewer 2:

Bias may have been introduced in the delivery of ‘usual care’ as health providers knew which group participants were allocated in, and therefore may have focused more on smoking cessation during consultations for those in the intervention (or usual care) group. The issue of contamination is also covered in the description of limitations, however it is not clearly stated why the health professionals delivering usual care needed to know who was randomised to which group [discretionary revision].

The reviewer is correct that failure of blinding of participants, researchers and healthcare providers may have influenced management of people based on their allocation. This is a unavoidable cause of contamination in health service research involving complex multi-dimensional interventions that are impossible to blind. In this case the concealment of random allocation is key and our study took significant measures to ensure this was the case. Health providers were not directly informed regarding study allocation. Due to the nature of the intervention the participants and research team were subsequently aware whether the participant belonged to the usual care or intervention group. Local healthcare staff may have been aware of this. (p7). However there was no difference in the extent to which the clinic was reported to provide advice to the two groups or in the prescription of NRT or other drugs to assist with smoking cessation between the two groups. This information has been included in the results (p11).

The recruitment of participants was opportunistic rather than random, however this is often the case in real world clinic and community settings in the provision of prevention activities, and those
recruited were later randomised to usual care or the intervention. However, the authors should provide a response rate of those approached to be in the study, who agreed and those who declined to participate [minor essential revision].

We used active as well as opportunistic recruitment and information about the study was widely disseminated. “Active recruitment was facilitated by the Aboriginal researchers through incidental encounters in the community, family and community links” (p6). It was not possible to record information about everyone who was informed about the study. The figure of 238 is the number assessed for participation (see Figure 1). This consists of all people who presented as interested in the study as well as clients who were referred by clinic staff.

The sentence in the results section “Of the participants classified as quit smoking at final follow-up, three (two usual care, one intervention) reported quitting after 12 months…usual care group.” This could be stated more clearly to help interpret the meaning. If the purpose of this section is to state that smokers in the intervention group quit sooner than those in the usual care group perhaps this could be stated more directly, or remind readers here that follow up for some participants occurred up to 3 months after the 12 month end point.

We have changed this to: Participants in the intervention group quit smoking sooner than those in the usual care group: all intervention group participants reported quitting at least two months before the final follow-up, as against only three of five in the usual care group.

The characteristics that favourably influenced the odds of quitting are an interesting component of the results, however it is not possible to interpret the meaning of these results given the width of the confidence intervals. Is therefore recommended that these results be removed from the paper [minor essential revision].

Removed as requested.

revision is to state clearly in the abstract and results the number (n) of participants who had quit in each group at final follow up alongside the proportions.

We have added this information to the abstract.

In Table 3, the second and third row are difficult to interpret at first read due to the distinction being in the footnote explanation. These rows to be more clearly labelled to distinguish to two [minor essential revision].

We have moved the information from the footnote to the table to more clearly distinguish the two results.

In order to be able to include the results for participants with complete outcomes data separately, some discussion of the follow-up process and reasons for loss to follow-up is required in the paper [minor essential revision]. Alternatively these results could be removed, and the authors just present self-reported quitting and urinary cotinine <50ng/ml assuming those lost to follow-up were still smoking.

We have added that: loss to follow-up was due to participants moving home and Aboriginal researchers not knowing where they moved to so they were unable to contact them. (p11)

Thank you once more for the opportunity to respond to the reviewers’ comments. We hope that the revision is satisfactory and that you are able to accept this article for publication in the BMC Public Health journal.

Yours sincerely

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Research Associate Professor