Author's response to reviews

Title: Smoking Cessation among Diabetes Patients: Results of a Pilot Randomized Controlled Trial in Kerala, India

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Author's response to reviews: see over
Dear Editor,

Thank you very much for giving us an opportunity to revise our manuscript and the excellent comments offered by the reviewers. We have attached a point by point reply to all the comments of the reviewers. In general we agreed to all the comments and the revisions are incorporated in the revised manuscript.

With warm regards
Yours Sincerely

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Reviewer 1

Major Compulsory Revisions

Comment 1:
Methods, Participants. There is no description of the power calculation describing what sample size the researchers were trying to achieve.

Reply:
We agree with the reviewer’s comment. Being a pilot study we decided to include all the patients who satisfied the inclusion criteria during the recruitment period. Post hoc power analysis based on the observed quit rates in the groups of size 98 each for an $\alpha$ error of 0.05 (or even 0.001), power was found to be about 100%.

We have added the following sentence in the revised manuscript in Page no 5, Line no 103-104.

“Being a pilot study we decided to include all the patients who satisfied the inclusion criteria during the recruitment period”.

Comment 2:
Methods, Study procedure. Please provide reference for the 5As and 5Rs counseling content.

Reply:
We have added a new reference “Fiore MC, Jaen CR, Baker TB, Bailey WC, Benowitz N, Curry SJ, Dorfman SF, Froelicher ES, Goldstein MG, Healton CG, Henderson PN: Treating tobacco use and dependence: 2008 Update. US Department of Health and Human Services, A Public Health Service 2009” for the 5As and 5Rs counseling content in Page no 5 Line no 88 of the revised manuscript.

Comment 3:
It is also necessary to know how often patients were seen to understand the intensity of treatment delivered. The results suggest monthly counseling, but this is not specified and I suspect the frequency of visits differs between early and experienced diabetics. Please
specify the number of visits and quantify volume of counseling received by subjects. Especially since a statement is later made about a dose-response relationship.

Reply:
The counseling was given three times (first contact, at one month and at three months). Each counseling section lasted about 30 minutes. The following modifications are made in the revised manuscript in Page no 7 Line no 144-147.

“Intervention–2 group patients received three diabetic specific tobacco counseling sessions (at first contact, at one month and at three months) lasting about 30 minutes in each session following the 5 ‘A’s (Ask, Advise, Assess, Assist and Arrange) and 5 ‘R’s (Relevance, Risks, Rewards, Roadblocks and Repetition)’.

Comment 4:
Methods, Follow-up of patients. The follow-up rate is more appropriately placed under results. Also, the last sentence is not clear. Both groups appear to have identical drop-out rates so I don’t understand what the six-month follow-up proportion was compared to.

Reply:
As suggested by the reviewer the follow up rates are placed under the result section of the revised manuscript in Page no10 Line no.222-224.

Although the follow up rate was similar in the intervention group-1 and the intervention group-2, the quit rate that we compared was different for the two groups.

The dropout rates at six month follow up was almost the same for the two groups. The following sentence was modified in the revised manuscript in Page no 8 Line no 184-186. “We reminded patients in both the groups by phone about the six month follow up in order to get maximum response”.

Comment 5:
Methods, Statistical analysis. Please specify whether one or two-tailed tests were used and introduce covariates of interest in the multivariable models. Also, this is a multivariable model, not a multivariate model.

Reply:
We have included the following sentences in the revised manuscript to incorporate the reviewer’s comments in Page no 9 Line no 196-197 & 200-201.

“Multivariable model using multiple logistic regression analyses were used to identify the correlates of quit rates”

“All the analyses were done using SPSS version 17.0 and statistical significance was set at two tailed p<0.05”

Comment 6:
Conclusion. No study of cost-effectiveness was performed; therefore the conclusion that this is a cost-effective way of reducing smoking may be true but was not tested or proven in this study.

Reply:
We agree with the reviewer’s comment. We have removed the word “cost effectiveness” in the revised manuscript in Page no14 Line no 325-328.

“Counseling sessions using disease specific diabetes messages and culturally sensitive use of the five ‘A’s and five ‘R’s cessation protocol is an efficacious way of reducing smoking, an important risk factor that significantly increases the chances of life threatening, debilitating and costly diabetes complications”.

Comment 7:
Table 2 and Table 3. Given the argument that there is a dose response relationship, you should control for volume of counseling through number of visits attended/counseling sessions received, as noted above.

Reply:
We agree with the reviewer’s comments and revised Table 2 and Table 3 by controlling for volume of counseling through counseling sessions received.

Modified Table 2 and Table 3 are presented in Page no 21 &22 Line No 441-453 of the revised manuscript. The corresponding revisions in the Odds ratios were made in the abstract of the revised manuscript in Page no 2 Line No 53-56.

“In the intention to treat analysis, the odds for quitting was 8.4 [95% confidence interval (CI): 4.1-17.1] for intervention-2 group compared to intervention-1 group. Even among high level smokers the odds of quitting was surprisingly similar. The odds of harm reduction was 1.9 (CI: 0.8-4.1) for intervention-2 group compared to intervention-1 group”.

Minor Essential Revisions

Comment 8:
Introduction. The authors do a nice job describing the magnitude of the problem in India in terms of prevalence of diabetes and tobacco use. However, other information needs more focus. The data about high out-of-pocket costs of diabetes care seem somewhat out of place in this study that does not evaluate the costs of their intervention. They either need to explain how smoking treatment reduces diabetes costs, expand the present analysis to include costs, or remove this information.

Reply:
We have removed the following sentence from the revised manuscript

“Diabetes care results in significant out of pocket expenditures. In the year 2000, the mean annual direct cost of outpatient care for diabetes patients was estimated to be Rs 4724
Comment 9:
Introduction. They offer some evidence of effectiveness/feasibility of this type of diabetic targeted intervention but don’t provide any of the general background of the effectiveness of behavioral therapy of this intensity. The effectiveness of counseling is well documented, if there is any information on counseling for tobacco cessation among diabetics in other settings, it would be useful to include.

Reply:
We have included the following sentence with a new reference in the revised manuscript in Page no 4 Line no 84-87.

“Results of a randomized controlled trial from the US found that smoking cessation intervention using motivational interviewing integrated into an established diabetes self management training program curriculum resulted in a trend toward greater abstinence at three months of follow-up in those receiving the directed smoking cessation intervention”.


Comment 10:
Methods, Participants. There is no description of the power calculation describing what sample size the researchers were trying to achieve.

Reply:
We agree with the reviewer’s comment. Being a pilot study we decided to include all the patients who satisfied the inclusion criteria during the recruitment period. Post hoc power analysis based on the observed quit rates in the groups of size 98 each for an α error of 0.05 (or even 0.001), power was found to be about 100%.

We have added the following sentence in the methods section of the revised manuscript in Page no 5 Line no 103-104.

“Being a pilot study we decided to include all the patients who satisfied the inclusion criteria during the recruitment period”.

**Comment 11:**
Methods, Participants. The recruitment rate is a study result not a method. Results should also report in more detail why subjects were excluded given that there are so many patients excluded.

**Reply:**
We agree with the reviewers comment. The following sentence is added in the result section of the revised manuscript in Page no 9 Line No 205-209.

“We screened 2490 male diabetic patients. Among them 363 (14.6%) were current smokers. Of these 363 patients, after excluding patients who were not willing to participate in the study (n=31), who were not the natives to the clinic catchment area (n=89) and who could not come for follow ups for the next six months (n=19), a total of 224 patients were included in the final study”.

**Comment 12:**
Methods, Follow-up of patients. Follow-up rates are more appropriately placed under results.

**Reply:**
We have added the following sentence in the results section of the revised manuscript in Page no 10 Line no 222-224.
“In the first follow-up wave (month one) we were able to contact 173 (77.2%) patients, in the second follow-up (month three) 163 (72.8%) patients and in the third follow-up (month six) 196 (87.5%) patients”.

Comment 13:
Methods, Statistical analysis. Justification for stratified analysis would be helpful. What was the hypothesis for the quit rates among different baseline levels of smoking?

Reply:
We have included the following sentence in the statistical analysis section of the revised manuscript in Page no 9 Line no 198-200.

“In order to test our hypothesis that high level smokers are more addicted to smoking and less likely to quit smoking compared to their low level smoking counterparts, we did a stratified analysis of baseline level smoking and quit rate at six months”.

Comment 14:
Results. No explanation is given for why the intervention worked among low and high but not medium level smokers.

Reply:
The intervention worked in medium level smokers also. We have added the following sentences in the revised manuscript in page No 11 Line no 248-252.

“Although the quit rates among low and high level smokers significantly increased in the intervention-2 group, the increase in quit rate among the medium level smokers did not achieve statistical significance probably due to small sample size. However, 72% of the medium level smokers shifted to low level smoking at the end of six months”.

Comment 15:
Results. The authors note a dose response rate with increasing quit rates over time. Treating tobacco use as a chronic disease with longitudinal rather than episodic care is important and it would be useful to compare the results with other longitudinal intervention studies.

Reply:
We agree with the reviewer. Tobacco use needs to be treated as a chronic disease. We have added the following sentence in the revised manuscript in the discussion section in Page no 13 Line no 292-294 with a new reference.

“It is important to treat smoking as a chronic disease understanding the nature of addiction, possibility of relapse and the need for continuum of care”.


Comment 16:
Limitations of the study. With a large proportion of diabetic smokers seemingly ineligible for the study, another limitation is that the results may apply to only specific smokers (male, literate, clinical care at the same site over 6 months).
- Discretionary Revisions

Reply:
We have modified the limitation section of the revised manuscript as follows in Page no 13 & 14 Line no 313-315.

“With a large proportion of diabetic smokers seemingly ineligible for the study, another limitation is that the results may apply to only specific smokers (male, literate, clinical care at the same site over six months)”.

Comment 17:
Methods, Study procedure. For others seeking to replicate this type of intervention, it would be helpful to have more detail about how diabetes educators were trained to provide tobacco treatment counseling.

Reply:
We have added a new sentence in the method section of the revised manuscript in page no 8 line no 178-180. “The counselors were subsequently given a certificate from the
University of Arizona after completing 15 brief intervention logs and passing an examination conducted by one of the authors (MN)“.

Comment 18:
Discussion, paragraph 2. Authors compare the counseling group to that of a similar program in Indonesia, but don’t do the same for the brief advice only (group 1) where there quit rate was much lower in Kerala than that found in Indonesia.

Reply:
We have added the better tobacco control program implementation in Kerala and modified one of the sentences in the revised manuscript under the discussion section. The revised sentence “This could be due to several factors, including the lower average number of cigarettes/bidis smoked per day in Kerala compared to Indonesia, the highly educated population in Kerala, better implementation of the national tobacco control program and the repeated 30 minutes counseling sessions for quitting each time the patient visited the clinic” is given in page no 12 line no 270-274.

Comment 19:
Table 2. Given potential bias in complete case analysis, would consider presenting only intent to treat results and deleting Table 2 since we do not know how the complete case groups differ.

Reply:
We could not follow up all the patients initially randomized in to both groups. This deviation from the original randomized groups can affect the comparison of two groups at the end of six month follow up. Thus considering every subject followed the original treatment assignment we did Intention to treat analysis as seen in most clinical trial studies. A perfect intention to treat analysis is possible only when the outcome of all participated in the study is known, irrespective of protocol deviation. Here, the outcome was not available for all the patients due to lost to follow up. We used an intention to treat analysis with an inherent assumption that all those who could not follow up did not quit. So we expect to get a conservative estimate and presented both the results of complete
case analysis and intention to treat analysis. We included both the results of complete case analysis and intention to treat analysis with the intention that some of the readers would interested to know both the results.
MINOR ESSENTIAL REVISIONS

Comment 1:
Abstract, Methods and findings, 2nd paragraph: “The primary outcomes WERE quit rate (seven day smoking abstinence) and harm reduction …”

Reply:
We agree with the reviewer’s comment. We have modified the sentence as follows “The primary outcomes were quit rate (seven day smoking abstinence) and harm reduction (reduction of the number of cigarettes / bidis smoked per day > 50% of baseline use) at six months”. in Page no 2 Line no 55-52

Comment 2:
Background, 1st paragraph: “The International Diabetes Federation in 2003[9] xxx have both strongly recommended that people with diabetes not TO smoke because …”

Reply:
We agree with the reviewer’s comment. We have modified the sentence as suggested by the reviewer

Comment 3:
Methods, Study procedure, 1st paragraph: “Smokers were identified by the counselor from this screening tool.’ Please describe what this screening tool is and how it works.

Reply:
The following sentence is included in the revised manuscript in Page No 6 Line No 119-121. “Smokers were identified by the counselor from this screening tool which inquired the patient’s smoking status”.

REVIEW II
Comment 4:
Methods, Study procedure, 2nd paragraph: “Subsequently the counselor randomized the patients equally …with block size four.” Please clarify the randomization procedure.

Reply:
Sequentially, every four patients enrolled were randomized into the two intervention groups using a computer generated random sequence to achieve a block size of four. We have added the following sentences in the revised manuscript in Page no 6 Line no 131-134

“Subsequently the counselor randomized the patients equally into two groups; intervention–1 and intervention–2 groups, with block size four. Sequentially, every four patients enrolled were randomized into the two intervention groups using a computer generated random sequence to achieve a block size of four, to facilitate interim analysis”.

Comment 5:
Methods, Study procedure, 3rd paragraph: “Intervention-2 group patients additionally got diabetic specific …”. Please give a brief description of the 5 ‘A’s and 5 ‘R’s approach.

Reply:
We have added the following reference (reference number 19) for the 5As and 5Rs counseling content in Page no 5 Line no 88 of the revised manuscript.


Comment 6:
Methods, Statistical Analysis: Correction for multiple testing should still be performed even the main findings will likely remain significant.

Reply:
Multiple tests were performed only because of the intention to treat analysis and complete case analysis where the sample sizes are different. Also in the bivariate analysis, all the ‘p’ values were larger than 0.05. So corrections were not considered.

Comment 7:
Results, Quit rate and harm reduction, 2nd paragraph:” The mean number of cigarettes/bidis smoked per day at month six …”. Was the p-value from the intention-to-treat analysis or complete-case analysis?

Reply:
The result presented was complete case analysis results. We have modified the sentence in the result section as follows in Page no 10 Line no 234-237.

“The mean number of cigarettes/bidis smoked per day at month six was 4 (SD 8.2) in the intervention–2 group, significantly lower (p < 0.001) than that of 10 (SD 13.7) in the intervention–1 group in complete case analysis”.

Discretionary Revisions
Comment 1:
Results, Quit rate and harm reduction, 3rd paragraph: “The quit rate among heavy smokers was surprisingly high (51.8%)”. The word ‘surprisingly’ should be changed to ‘significantly’ high, and there should be a paragraph discussing this surprise in the discussion.

Reply:
We agree with the reviewer. We have modified the sentence as follows in Page no 11 Line no 247-248.

“The quit rate among heavy smokers was significantly high (51.8%)”

Comment 2:
Discussion-please comment on the discrepancies of results obtained between complete case versus intention-to-treat approach. For example, why did the authors choose to perform both types of analysis?
Reply:
We could not follow up all the patients initially randomized into both groups. This deviation from the original randomized groups can affect the comparison of two groups at the end of six month follow up. Thus considering every subject followed the original treatment assignment we did Intention to treat analysis as seen in most clinical trial studies. A perfect intention to treat analysis is possible only when the outcome of all participated in the study is known, irrespective of protocol deviation. Here, the outcome was not available for all the patients due to lost to follow up. We used an intention to treat analysis with an inherent assumption that all those who could not follow up did not quit. So we expect to get a conservative estimate and presented both the results of complete case analysis and intention to treat analysis.