PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Linkage to care among adults being investigated for tuberculosis in South Africa: pilot study of a case manager intervention
AUTHORS	Maraba, Noriah; Chihota, Violet; McCarthy, Kerrigan; Churchyard, Gavin; Grant, Alison

VERSION 1 – REVIEW

REVIEWER	Nesri Padayatchi CAPRISA, South Africa
REVIEW RETURNED	20-Dec-2017

GENERAL COMMENTS	In this study the data comes from 5 clinics, however it is not clear how the clinics were selected. If the clinics were selected at random, the data would need to be treated as arising from a cluster sample with each clinic being a separate cluster. Appropriate statistical techniques for the analysis of cluster survey data would then need to be used to report findings, including weighted average prevalences. In the results section the denominator changes and it is confusing or difficult to keep track of the percentages. It would therefore be preferable to report the numerator, denominator and percentages (% (n/N)) in the text. Table 1, page 11, symptoms reported: The percentages are incorrect and needs to be revised. Also, the percentages need to be consistent and rounded off by either 1 or 2 decimal places. This needs to be revised throughout the results section. For example: • Page 9, line 189 should be (209[6.7%]) instead of (209[6.9%]) • Page 14, Table 1, line 11, female (17/307) is 5.5% and not 6.9% • Table 1, line 24, Negative (5/130) is 3.8% and not 3.9% Page 12, paragraph 2 refers to 94 participants that needed an HIV test. There is no clarity as to where the 94 participants came from. It would have been useful to see the predictors of linkage to HIV care since the denominator is sufficient to run a model. Could age, gender or income play a role? It is good that the authors were careful not to over fit the logistic model as this could cause misleading estimates and p-values.

REVIEWER	Ingrid V. Bassett, MD, MPH Massachusetts General Hospital, Harvard Medical School, USA
REVIEW RETURNED	05-Jan-2018

GENERAL COMMENTS	This single-arm pilot study sought to evaluate the feasibility, acceptability and preliminary efficacy of a case management intervention delivered by lay counselors for improving linkage to HIV and TB care for individuals being evaluated for TB in 6 primary health clinics in South Africa. Counselors contacted participants by phone and/or in person at least once per week to inform participants of test results, remind them of clinic appointment and to check in on whether patients had returned for care. Study outcomes were linkage to HIV care, defined as having a CD4 count and ART initiation within 3 months for those eligible and linkage into TB care, defined as TB treatment initiation within 28 days from sputum specimen submission for those Xpert MTB/RIF+. Outcomes were by self-report and patient clinic file confirmation via professional nurse. Participants were classified as needing HIV linkage, TB linkage, or both. Mortality was ascertained via close friends or relatives. This study seeks to address the critical problem of improving linkage to HIV and/or TB in public sector clinic sites in South Africa. In general, the paper is clearly written and the conclusions follow logically from the results. The authors point out the major weakness, which is a lack of comparator group, which limits making conclusions about intervention efficacy, however, there is value to presenting the details of this pilot for developing future interventions. The authors detail the intensity of the intervention, in terms of the number of contact attempted and successfully made, which is an important consideration for implementation. Some suggestions which could strengthen the manuscript: 1. It would be helpful to give a definition of the potential pool of participants – "those needing TB investigations" can cover a broad range of scenarios (symptoms, abdominal mass, pleural effusion, HIV positive, etc) 2. The outcomes measured as described in the methods are linkage, but the results are presented as non-linkage. For clarity, it would be helpful to match the methods and results. 3. The opening of the manuscript talks about linking to HIV care for people being investigated for TB, but the references in the subsequent section are not specifically about HIV/TB, which was a bit confusing. 4. Why kind of training did the lay counselors receive? Did they get support for maintain lists of who still needed contacting? 5. Were the case managers introduced to the patient at enrollment? Were they introduced in person? It was somewhat confusing how in person contacts with patients were made – did the lay counselor look for the patient in the waiting room? 6. For "adequate locator information" as an inclusion criterion– did this include alternative (family/friend contacts)? This is important for the mortality ascertainment, which may be under-reported in this study. Would consider that a potential limitation in this study. 7. The XTEND trial involved study staff contacting patients after enrollment – was any of that infrastructure left behind? That is, were others (such as a TB nurse) contacting patients in addition to the lay counselors? 8. In baseline characteristics, consider mentioning that 17% were previously treated for TB. This seems important in understanding the patient population and their prior experience. 9. I don't think risk factors for mortality are that relevant. With no comparator group, no SA ID number verification and small

	number of deaths, this seems like a stretch. And it's not mentioned in the abstract or discussion of the paper. 10. In the discussion, it seems worth considering in more detail how this case management intervention differed from those that were successful in terms of staffing, training and components. For example, the ARTAS study (referenced in the paper) used in person contacts and a more trained navigator than a lay counselor. The Ugandan study referenced in the paper had a strong training and coaching component and was a multicomponent intervention, including facility feedback. The Tanzanian and Zambian study had weekly home visits. It may be that a higher intensity intervention than the one presented here would be more effective.

VERSION 1 – AUTHOR RESPONSE

Thank you for reviewer's comments
Reviewer 1 Comment 1
In this study the data comes from 5 clinics, however it is not clear how the clinics were selected. If the clinics were selected at random, the data would need to be treated as arising from a cluster sample with each clinic being a separate cluster.

Appropriate statistical techniques for the analysis of cluster survey data would then need to be used to report findings, including weighted average prevalence's.

Response:
Our study was not a cluster randomized trial (CRT) but rather an interventional cohort study. The current study was however conceptualised after the completion of a large CRT called the XTEND trial. At the end of the XTEND trial, clinics that had participated in the trial and had reported high proportions of pre-treatment loss to follow-up were selected to be part of our interventional cohort study. This is now stated in (page 5, line 97-98).

Our study was not a CRT, therefore we did not need to use statistical techniques for cluster survey data to report our findings.

Reviewer 1 Comment 2
In the results section the denominator changes and it is confusing or difficult to keep track of the percentages. It would therefore be preferable to report the numerator, denominator and percentages (% (n/N)) in the text.

Response:
We have reported on numerators, denominators and percentages in results section from page 9-13 to avoid confusion.

Reviewer 1 Comment 3
Table 1, page 11, symptoms reported: The percentages are incorrect and needs to be revised. Also, the percentages need to be consistent and rounded off by either 1 or 2 decimal places. This needs to be revised throughout the results section. For example:

- Page 9, line 189 should be (209[6.7%]) instead of (209[6.9%])
- Page 14, Table 1, line 11, female (17/307) is 5.5% and not 6.9%
- Table 1, line 24, Negative (5/130) is 3.8% and not 3.9%

Response
Percentages in symptoms reported variable in Table 1 on page 11 have been revised.

Percentages on Page 9, line 197 has been retained as [63.9%] as it is 209 of 327 participants with a known CD4 count) this has now been explained much clearer in the manuscript. On Page 14, Table 2, female (17/307) has been changed to 5.5%. Table 2, Negative (5/130) has been changed to 3.8%. We also checked the rest of the percentages in both table 1&2 as well as the results section throughout the manuscript for consistency and rounded them off to 1 decimal place.

Reviewer 1 Comment 4
Page 12, paragraph 2 refers to 94 participants that needed an HIV test. There is no clarity as to where the 94 participants came from.

Response:
The 94 participants needing an HIV test were participants that did not know their HIV status at enrolment which was described as an unknown HIV status or negative HIV test results older than three months at enrolment to test as stated in page 6 line 108-110. We have however put an additional sentence on page 12 line 235-237 to clarify were these participants come from.

Reviewer 1 Comment 5
It would have been useful to see the predictors of linkage to HIV care since the denominator is sufficient to run a model. Could age, gender or income play a role?
It is good that the authors were careful not to over fit the logistic model as this could cause misleading estimates and p-values.

Response:
Linkage to HIV care in our study was defined as either i) getting a CD4 count test done after an HIV positive result ii) being started on ART if eligible (CD4 count ≤ 350 cells/mm3 or testing Xpert MTB/RIF positive. Patients in our study could enter the HIV linkage to care pathway at any stage resulting in different denominators for each stage. Among those having HIV test done (n=68), 26 were HIV positives. Of those needing a CD4 count (n=132), 119 had a CD4 count done and lastly of the 91 that were ART eligible, 67 initiated ART. For us to build a model, we would have to build it for one stage at a time which is not consistent with our definition of linkage to HIV care in our study. With these it would therefore be complicated for us to build a model for linkage to HIV care.

We did however do an analysis for the ART initiation stage, exploring predictors of ART initiation (table shown below) and none of the socio-economic factors were statistically significant at p value < 0.1 in the univariate model and we therefore could not run a multivariate model. We therefore decided it would not be necessary for us to include this analysis in the manuscript.

Univariate analysis for factors associated with ART initiation

Variable	*Proportion initiated on ART (%)*	*OR (95% CI)*	*P value*
Gender			
Male	*35/49 (71.4)*	*1*	
Female	*32/42 (76.2)*	*1.28 (0.49-3.29)*	*0.60*

Age group			
>30	*18/25(72.0)*	*1*	
30-39.9	*24/36 (66.7)*	*0.77 (0.25-2.37)*	
≤40	*25/30 (83.3)*	*1.94 (0.53-7.12)*	*0.29*
Marital status			
Single	*38/51 (74.5)*	*1*	
Married	*4/9 (44.4)*	*0.27 (0.06 – 1.18)*	
Cohabitating	*19/23 (82.6)*	*1.63 (0.47 – 5.66)*	
Divorced/widowed/separated	*6/8 (75.0)*	*1.02 (0.18 – 5.73)*	*0.21*
Highest education completed			
Pre-school –Grade 7	*14/20 (70.0)*	*1*	
Grade 8-12	*48/64 (75.3)*	*1.28 (0.42-3.91)*	
Post-high school	*5/7 (71.4)*	*1.07 (0.16-7.15)*	*0.89*
Income			
< ZAR 600	*3/5 (60.0)*	*1*	
ZAR 601-1000	*10/16 (62.5)*	*2.4 (0.89 - 6.45)*	
ZAR 1001-2000	*17/23 (73.9)*	*1.8 (0.25-14.19)*	
ZAR 2001-4000	*19/28 (67.9)*	*1.40 (0.19-9.96)*	
Greater than ZAR 4000	*6/6 (100)*	*-*	
Don't know	*12/13 (92.3)*	*8 (0.53-120.64)*	*0.32*

Reviewer 2 Comment 1
It would be helpful to give a definition of the potential pool of participants – "those needing TB investigations" can cover a broad range of scenarios (symptoms, abdominal mass, pleural effusion, HIV positive, etc)

Response:

Patients that needed TB investigations were those who were identified by health care workers through a TB symptom screen as having any of the four TB symptoms and having provided a sputum sample for TB testing. This is now stated on page 6 line 130-131 to provide clarity

Reviewer 2 Comment 2
The outcomes measured as described in the methods are linkage, but the results are presented as non-linkage. For clarity, it would be helpful to match the methods and results.

Response:
We have defined both linkage and non-linkage in the outcomes section (page 7 & 8, line 147-158) and furthermore presented the results according to both linkage and non-linkage to care in the manuscript (page 12, line 235-250). Under the heading: Implementation of the intervention (page 11, line 210), we showed implementation of the intervention in the overall group and also in the 3 linkage groups (HIV, TB and both) but also further expanded on the contact attempts made to those who did not link into care. For clarity sake, we also re-worded the headings in line (219,224 and 228) from just linkage to TB, HIV or both to be contact attempts for linkage into TB, HIV or both.

Reviewer 2 Comment 3
The opening of the manuscript talks about linking to HIV care for people being investigated for TB, but the references in the subsequent section are not specifically about HIV/TB, which was a bit confusing.

Response:
We agree that the sentence is confusing. We have changed to be “people being investigated for TB are not linking into TB and HIV care on page 4 line 58.

Reviewer 2 Comment 4
Why kind of training did the lay counselors receive? Did they get support for maintain lists of who still needed contacting?

Response
The case manager (lay counsellors) were trained by a TB clinician who was part of the investigators team, on basic TB and HIV education as well as national ART and TB management guidelines. This is now stated on page 5 line 104-105. The smart phone application that was used to collect data would automatically require that case manager complete weekly follow-up case reports for all patients enrolled until they are linked into care. This therefore assisted them in maintaining a list of who still needed to be contacted. This is now indicated on page 6 line 116-119.

Reviewer 2 Comment 5
Were the case managers introduced to the patient at enrollment? Were they introduced in person? It was somewhat confusing how in person contacts with patients were made – did the lay counselor look for the patient in the waiting room?
Response:
Once a patient at a facility was classified as needing TB investigation by clinic nurses, they provided a sputum for TB testing and they were also referred to case managers so they would be offered an opportunity to participate in the study. The case managers would then enrol those who were interested in taking part in the study as well as facilitate their linkage into care indicated on page 7 line 134 & page 5-6 line 106-112. In some cases, patients would be in the clinic when contact attempts were being made and they would go to the case manager to report on their linkage progress and also get guidance on what to do next.

Reviewer 2 Comment 6

For “adequate locator information” as an inclusion criterion– did this include alternative (family/friend contacts)? This is important for the mortality ascertainment, which may be under-reported in this study. Would consider that a potential limitation in this study.

Response
Yes, locator information in our study included contact details of alternative family member or friend in case we could not get hold of the participant. This is now indicated in line 133-134 on page 7.

Reviewer 2 Comment 7
The XTEND trial involved study staff contacting patients after enrollment – was any of that infrastructure left behind? That is, were others (such as a TB nurse) contacting patients in addition to the lay counselors?

Response
The case managers were study staff supporting TB nurses at the clinics by contacting patients (so they initiate on relevant treatment if needed) and at the end of the study the TB nurses would have taken over this role. None of the XTEND trial staff were left behind to assist in the implementation of this study. In our study, lay counsellors were the only group of staff that were in contact with the participants. Nurses were only hired to do patient file abstractions at the end of 3 months follow-up and were not in contact with the patients as stated on page 7 line 142-144.

Reviewer 2 Comment 8
In baseline characteristics, consider mentioning that 17.1 % were previously treated for TB. This seems important in understanding the patient population and their prior experience.

Response:
Statement has been included on page 9 line 198.

Reviewer 2 Comment 9
I don’t think risk factors for mortality are that relevant. With no comparator group, no SA ID number verification and small number of deaths, this seems like a stretch. And it’s not mentioned in the abstract or discussion of the paper.
Response
We decided to keep Table 2 because this population is often at high risk of death especially before a diagnosis is made and it was interesting to explore factors associated with death.
Reviewer 2 Comment 10
In the discussion, it seems worth considering in more detail how this case management intervention differed from those that were successful in terms of staffing, training and components. For example, the ARTAS study (referenced in the paper) used in person contacts and a more trained navigator than a lay counselor. The Ugandan study referenced in the paper had a strong training and coaching component and was a multicomponent intervention, including facility feedback. The Tanzanian and Zambian study had weekly home visits. It may be that a higher intensity intervention than the one presented here would be more effective.

Response
The differences between this intervention and the two interventions referenced were highlighted on page 16 line 315-319.

VERSION 2 – REVIEW

REVIEWER	Ingrid V. Bassett, MD, MPH Massachusetts General Hospital Boston, MA

	USA
REVIEW RETURNED	30-Mar-2018

GENERAL COMMENTS	The authors have been responsive to the initial review.