Im*pro*ving TB outcomes by modifying *life*-style behaviours through a brief motivational intervention (PROLIFE), V09

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Key Words: TB treatment; Brief Motivational Interviewing (BMI); Tobacco smoking; Alcohol use; Treatment adherence; HIV or HIV/TB co-infection

Table of Contents

1. Executive Summary/Abstract

One in four tuberculosis (TB) deaths in South Africa could be prevented if tobacco smoking were eliminated and 10% of the global burden of TB is attributable to alcohol use. Both smoking and harmful alcohol use in TB patients have been associated with poor drug adherence and low treatment success. Furthermore, if TB patients are also co-infected with HIV, non-initiation of antiretroviral treatment (ART) or poor adherence to ART increases the risk of adverse effects and death. Alcohol and/or tobacco smoking are common among TB patients in South Africa. Moreover these lifestyle behaviours occur more often among men who are at greater risk of late care seeking for HIV. Therefore addressing these lifestyle behavioural risk factors in an integrated way could improve TB treatment outcomes. Such an intervention may also impact on the transmission of TB, as family members of smokers, children in particular, are more likely to acquire TB than those of non-smokers.

We aim to develop a complex behavioural intervention, the PROLIFE model comprised of a brief motivational interviewing (MI) counselling strategy augmented with subsequent text messaging. To be delivered in multiple brief sessions, the MI intervention will target several areas, as appropriate: **tobacco smoking (T), alcohol drinking (A**) and **TB and ART adherence or ART initiation (TA).** The PROLIFE model - building on our earlier success of a trial of MI for smoking cessation in TB patients, will be evaluated through a pragmatic, prospective, two-arm cluster randomised control trial (cRCT) in primary health care clinics (PHC) located in high TB burden communities in three provinces in South Africa. The theoretical model on how this intervention will impact on pulmonary TB (PTB) outcomes is outlined in Figure 1 at the end of this proposal. We aim to achieve the following:

- Goal 1: To **develop the PROLIFE model consisting of brief MI augmented with text messaging** for promoting improved PTB outcomes through the Tobacco-Alcohol-TB treatment and ART package.
- Goal 2: To estimate the **effectiveness of the PROLIFE model** delivered by lay health workers (LHWs) versus usual care in improving PTB treatment outcomes.
- Goal 3: To estimate the **cost-effectiveness** of the PROLIFE model.
- Goal 4: To conduct **process** evaluation relating to the design and delivery of the PROLIFE model.
- Goal 5: To identify the **key barriers and facilitators** affecting the implementation of the PROLIFE model and **propose a wider implementation plan.**

This project will be underpinned by a robust implementation science approach which will include a longitudinal process evaluation based on the MRC's evaluation framework for complex interventions with analysis guided by the normalization process theory. This framework will ensure that the PROLIFE model of delivery is fully cognisant of the contextual barriers and facilitators to implementation before, during and after the cRCT, in order to enable scaling up of the PROLIFE model to other areas of South Africa, as well as the translation of the model to other Sub-Saharan African countries. It will also ensure the buy-in and involvement of clinicians, LHWs, patients, health service managers and policy makers, and that the value of the model from multiple perspectives is taken into account. PROLIFE involves an international, multidisciplinary team, including researchers in TB, public health and policy, implementation science, addiction research, health services research, primary care, health economics, mHealth, and government. An important strength of the team is the involvement of local and international stakeholders and experts, including researchers from the University of York and the University of East Anglia in the UK, the University of Pretoria, the University of Cape Town, the University of the Free State and national and provincial government officials from the Department of Health.

2. Introduction

South Africa has the third highest TB burden in the world.[1] Moreover TB treatment success rates are low due to high treatment interruption, drug resistance and death.[1] HIV-positivity is one of the most important risk factors for death in TB patients, but early ART initiation greatly reduces this risk.[2] Integration of TB and HIV services has therefore been prioritised in recent years.[1] However, less attention has been paid to the multitude of social, behavioural, structural and clinical factors that impact individuals' chances of successful TB treatment. Tobacco use and problem drinking are prevalent in TB patients[3-5] and are known to increase the risk of death and poor treatment adherence.[6-9] Furthermore in TB patients, tobacco smoking and problem drinking often co-occur, are associated with poverty and depression and are more common in men.[4,5] Men also delay TB treatment and ART more often.[7,10] Although 90% of patients were tested for HIV in SA in 2013, only 66% of the HIV-positive patients were on ART.[1] This figure is likely to be lower for TB patients who smoke or drink.[11] Smoking not only increases the risk for TB infection and progression to disease,[12] but has also been shown to increase the risk of isoniazid resistance,[13] and to increase the risk of treatment failure[14] and of relapse.[15,16] Both excessive drinking and tobacco smoking adversely affect TB treatment and ART adherence.[6-9,16,17] Moreover, second-hand smoke may increase the risk for TB disease and spread of TB in households and public spaces.[18] Tobacco smoking also leads to a myriad of HIV-related complications.[19]

Addressing smoking and alcohol misuse in TB patients has some distinct short- and medium-term advantages. For example, most of the immunological abnormalities in TB patients induced by smoking tobacco are reversible within six weeks of stopping smoking.[20] Among TB patients, smoking cessation could reduce the risk of death due to TB by more than half.[21] Furthermore a recent study demonstrated that patients who had recently stopped smoking had a lower risk of a poor TB outcome than current smokers.[22] Majority of TB patients in South Africa are co-infected with HIV; therefore tobacco cessation in HIV-TB co-infected patients may reduce TB deaths through its beneficial effects on – amongst others- lower respiratory tract infections.[19] Brief smoking cessation interventions are effective and affordable in low-income countries, both in TB patients and in general smokers.[23,24] Furthermore the theory of 'teachable moments' explains why TB patients are more likely to be amenable to health promotion advice and to succeed in quitting smoking and moderating alcohol use, compared to general smokers and problem drinkers.[25]

Integrating TB control efforts with non-communicable disease efforts has been advocated by leading scientists.[26,27] While several studies attempted to evaluate the individual effectiveness of tobacco cessation, alcohol reduction or adherence interventions in TB patients,[28,29] only a few studies reported on complex interventions to improve TB treatment outcomes.[28,30,31] To our knowledge, no study used an approach of patient-centered counselling to address multiple behavioural problems that negatively impact TB outcomes. Motivational Interviewing is a counselling technique with demonstrated effectiveness for the reduction of hazardous drinking, tobacco cessation and TB treatment and/or ART adherence.[23,33-35] We have already demonstrated that MI is efficacious in smoking cessation and can be delivered by trained LHWs.[36] ART adherence and tobacco cessation can also be enhanced with mobile phone technology.[37] It may also increase TB treatment adherence but there are currently insufficient data on its effectiveness and further studies are warranted.[38] PROLIFE will use traditional phones to enable adherence to treatment through SMS reminders, but to also support smoking and alcohol cessation.

In conclusion the PROLIFE aims to significantly improve TB outcomes in South Africa and beyond.

3. Study Goals

- Goal 1: To **develop the PROLIFE model consisting of brief Motivational Interviewing augmented with text messaging** for promoting improved PTB outcomes through the Tobacco-Alcohol-TB treatment and ART package.
- Goal 2: To estimate the **effectiveness of the PROLIFE model** delivered by lay health workers (LHWs) versus usual care in improving PTB treatment outcomes.
- Goal 3: To estimate the **cost-effectiveness** of the PROLIFE model.
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4. Study Setting

The study will be undertaken in three districts in three South African provinces: Lejweleputswa in the Free State, Bojanala in the North West province and Sedibeng in Gauteng province. TB clinics in those sites will listed according to the TB workload and the availability of lay HIV counsellors or lay TB health workers at the clinic. The 40 clinics with the largest pulmonary TB workload will be randomised into intervention or control clinics for the purpose of the Randomised Controlled Trial (Goal 2).
The development of the Prolife model (Goal 1) will be executed in the clinics excluded from the trial. More specifically: focus group discussions will be held with TB patients and LHWs at clinics excluded from the trial. Similarly the piloting of the MI and SMS-intervention will be done at those clinics.

5. Methodology (presented separately for each goal)

Goal 1. To develop the PROLIFE model consisting of brief MI augmented with text messaging for promoting improved PTB outcomes through the Tobacco-Alcohol-TB treatment and ART package

A formative stage will be conducted to inform the refinement of the PROLIFE model and the development of an MI Counselling manual and the SMS-package, as well as to inform researchers on the implementation processes of the PROLIFE intervention.

The following methods will be used in the formative phase:

a) Focus group discussions

Each of the 3 research sites (Lejweleputswa in the Free State, Bojanala in the North West province and Sedibeng in Gauteng province) will hold focus group discussions with male and female TB patients who smoke and/or drink and with LHCWs (3 focus groups for each research site, i.e. 9 in total).

For the purpose of the focus group discussions with LHWs, eligibility criteria for LHWs will be: a minimum of 1 year experience in lay health work, work in the field of HIV or TB and completion of the phase 1 training for LHWs required by the National Department of Health of South Africa.

For the focus group discussions with TB patients, patients will be eligible if they adult TB patients who are current smokers or hazardous/ harmful drinkers.

The interview guides for the different focal areas are based on the Information-Motivation-Behaviour Skills model of TB adherence as described by Iribarren et al. (Journal MTM 3:2:16-27, 2014) and adapted from Fisher et al. 2006 and Munro et al. 2007 (Appendix 4). Focus group discussions will be facilitated by skilled facilitators from the Centre for Health Research and Development of the UFS who provide academic oversight and by researchers from the other universities involved in the Prolife project. Interviews and discussions will be audio-recorded and transcribed verbatim. For the interviews and discussions conducted in seTswana, seSotho or isiZulu, the written transcripts will be translated into English. All data will be thematically analysed drawing both from a-priori codes informed by the IMB tool and relevant literature, as well as inductive codes derived from raw data. Information derived from focus groups will be used to modify the intervention package as needed before the actual trial starts.

b) Semi-structured interviews with health care managers

The aim of the semi-structured interviews will especially be to 1) help inform the intervention towards a more culturally sensitive programme, and 2) assess the readiness of targeted PHC clinics to adopt the planned intervention. Eleven semi-structured interviews will be held with managers involved in TB care as listed below:

- 3 district TB managers (Bojanala, Lejweleputswa and Sedibeng district managers)
- 6 clinic managers (2 per district)
- 3 provincial TB managers (FS, NW and Gauteng)
- 1 national TB manager

The interview guide is based on Normalisation Process Theory and is attached as Appendix 5. Interviews and discussions will be audio-recorded and transcribed verbatim. Semi-structured interviews will be facilitated by skilled facilitators from the Centre for Health Research and Development of the UFS. All data will be thematically analysed drawing both from a-priori codes informed by the Normalisation Process Theory tool and relevant literature, as well as inductive codes derived from raw data.

c) Brief MI intervention package development and evaluation of training

The MI manual will be developed through literature review and a four day expert review workshop with researchers from SA and York University which will be held as soon as the funding has been obtained.

We will identify 3 LHWs per district who are currently not employed as LHWs and approach them for their willingness to be employed for the duration of the study as lay counsellors. The will be chosen from geographically distant areas within the district (preferably from the major sub-districts). To be eligible they should have passed grade 12 and have successfully completed the phase 1 training for LHWs (NQF3). If agreeable, they will be trained in a 5 day workshop on MI techniques and problem drinking, tobacco cessation and TB and antiretroviral treatment adherence. They will also be trained in the contents of the educational

SMS messages and the SMS system that will be developed for this study. Their pre- and post-test knowledge will be determined using standardized questionnaires, with Likert-type questionnaires at the beginning and at the end of the 5-days workshop (Appendix 6).

Differences in scores will be calculated used paired t-tests or Wilcoxon sign-rank tests (as appropriate). Additional training will be provided in year 2 before the start of the actual trial, as required, based on gaps identified in knowledge and skills in year 1 and issues identified from focus group discussions and the piloting process (see below).

d) Development of SMS–package

The educational content of the SMS system will be based on the Information-Motivation-Behaviour Skills model. The most suitable messages will be identified and/or developed from a combination of literature review and developed in the expert review workshop. For example, for the tobacco cessation messages, we will select and adapt messages from the library of text messages developed by the World Health Organisation on tobacco cessation (WHO Library Cataloguing-in-Publication Data. A handbook on how to implement Tobacco Cessation, 2015). Messages will also be adapted - as required- on the basis of themes arising from the focus groups discussions with patients at a later stage.

Once suitable messages have been identified they will be culturally adapted, translated in the most common local languages and formatted to be suitable for the character limitations of SMS messages. Written messages will be supplemented with voice messages as some patients may be illiterate. The message delivery order and adaptation to the needs of the patients (i.e. smoker vs. drinker or both) will also be an important consideration. Messages will be delivered twice a week over 12 weeks (for 4 weeks after the baseline MI, for 4 weeks after the 1-month MI and for 4 weeks after 2-month MI session) reinforcing the MI session received prior to this. The intervention will be piloted with 3 patients for each LHW (see subheading e below).

Staff members from the private company providing the SMS and data management system (Mobenzi) will collaborate with the research team to provide the SMS technology for SMS-reminders and the technology needed for field research and data collection. Mobenzi has a track record of working with academics and has successfully deployed similar technology across South Africa and elsewhere.

e) Piloting of the MI intervention and SMS-package with real-life TB patients

The MI intervention will be piloted with 3 TB patients for each LHW (i.e 9 x 3 patients who will each receive 3 MI sessions, therefore 81 MI sessions).

Study setting

The piloting study will take place at 9 clinics excluded from the list of the trial clinics (3 clinics per district). The LHWs trained in the Prolife package (as explained earlier) will deliver the Prolife package to the TB patients who will be identified by a fieldworker placed at each of the 9 piloting clinics.

Eligibility criteria for the TB patients

The participants will be adult TB patients who initiate treatment (or who have been on treatment for less than one month for this TB episode) for drug sensitive pulmonary TB (PTB) - bacteriologically or clinically confirmed (diagnosis according to the National TB guidelines). Only current smokers (defined as having smoked any tobacco in the past month) and/or hazardous or harmful drinkers, but not dependent drinkers (alcohol used disorders identification test [AUDIT] score ≥ 8 for men or ≥ 7 for women and ≤ 20) will be eligible. Furthermore patients must be in possession of a functioning cell phone. Participants who are too ill to be interviewed

or who do not speak any of the languages in which the questionnaires will be provided (English, isiZulu, SeSotho and Setswana) will be excluded from the study.

After the administration of a screening questionnaire (Appendix 7) to identify eligible patients, each patient will be asked for consent and will – by appointment- receive 3 MI sessions: after enrolment, at one month follow-up and at two months follow-up. All reasonable attempts will be made to have the appointments for TB treatment scheduled on the same day as appointments for MI counselling.

In the initial MI session at the start of TB treatment the LHW will establish rapport and the participant's tobacco smoking, problem drinking and other potential obstacles and facilitators for treatment adherence or initiation (both TB and ART treatment) will be determined. This first session will be concluded with agenda setting for the problem identified by the participant, as the most salient. This could be a plan either to quit tobacco smoking, reduce drinking or deal with other perceived obstacles relating to ART or TB treatment. As all TB patients are eligible for ART, for participants who are HIV-infected and not yet on ART, beliefs and attitudes regarding HIV-testing or ART will be explored to facilitate ART initiation and adherence." The second session will build on the previous one and deal with challenges relating to the previous agenda setting, but then move on to the next behavioural problem (T, A or TA) where applicable. The third session will deal with the last identified problem. These individual counselling sessions will be re-enforced with SMS-based reminders regarding information supporting tobacco cessation, alcohol use and treatment adherence. Text messages will be delivered twice a week over 12 weeks and pre-tested as outlined above. Patients will receive a prompt to send a confirmation upon receiving a message and thus there will be a record of fidelity.

The MI-intervention will be tape-recorded and the fidelity of the intervention determined against a MI-intervention fidelity tool developed by the research team based on existing tools. One TB patient will be randomly selected from each LHW for review of intervention fidelity. This audio-taped session will be evaluated by two MI-experts who will rate the sessions independently. Inter-rated reliability will be determined, as well as average scores for the selected MI sessions.

Patients and LHWs will be interviewed once post-MI (after the third MI session for the patients and after the second completed patient MI series for the LHWs?) to explore barriers and facilitators relating to the MI and the SMS-messaging system with the aid of a brief semi-structured questionnaire (Appendix 8 and 9). Interviews will be tape recorded and open questions transcribed and thematically analysed. Fieldworkers will administer these questionnaires as well the consent forms.

Quantitative data derived from structured questionnaires will be analysed with Stata Statistical package version 14. Data analysis will consist of descriptive analysis with percentages, means and SD and medians and interquartile ranges, as appropriate. Open questions will be analysed by transcribing the answers to this questions, coding and iterative thematic analysis.

f) Validity, reliability, trustworthiness

For both the focus group discussions and the semi-structured interviews, the transferability and credibility of the data will be enhanced by means of member checking. Data transcripts will be checked with a portion of participants within each targeted group to check for accuracy. Reliability and trustworthiness will be achieved by means of triangulation of the data among 1) LHWs and patient focus group data and 2) different management level semi-structured interview data, while the MI intervention pilot evaluation will also be enhanced by the LHW and patient focus group data. Further, during data analysis, multiple coding and iterative thematic

analysis in terms of independent team members coding the data and comparing results will be done to preserve the interpretive validity of inferences. Inter-rater agreement of findings and themes will occur across the three sites.

Goal 2. To estimate the effectiveness of the PROLIFE intervention delivered by LHWs in improving PTB treatment outcomes versus usual care.

Goal 2-5 will be implemented only on successful implementation of Goal 1. Detailed instruments for these goals will be submitted to the relevant ethics committees after year 1 (as an amendment to the protocol). Goal 2 consists of a cluster randomised controlled trial to determine the effectiveness of the Prolife package and is graphically presented in Figure 1.

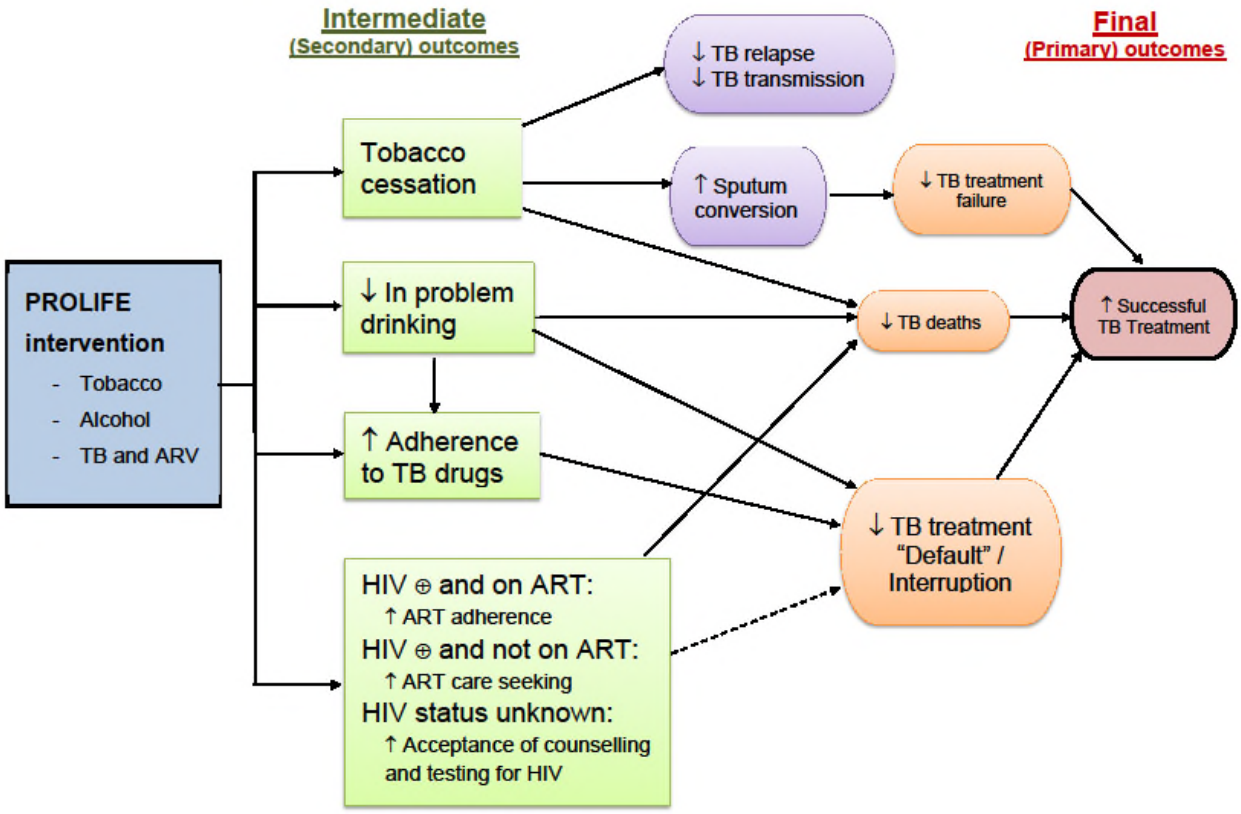

Figure 1. Theoretical model of intervention impact on PTB treatment outcomes

Design: Pragmatic cluster randomised controlled trial with TB clinics as the randomisation unit and outcomes assessed at individual patient level

Setting: The study will take place at the 40 primary care clinics with the highest TB case load in three districts in 3 South African provinces (Lejweleputswa in the Free State, Bojanala in the North West province and Sedibeng in Gauteng province). Clinics not willing to participate will be excluded from the study.

Participants: The participants will be adult TB patients who initiate treatment (or who have been on treatment for less than one month) for drug sensitive pulmonary TB (PTB) - bacteriologically or clinically confirmed. Only current smokers (defined as having smoked any

tobacco in the past month) and/or hazardous or harmful drinkers who are not alcohol dependent (alcohol AUDIT score ≥ 8 for men or ≥ 7 for women but ≤20) will be enrolled in the trial. It is estimated that 20% of participants will be smokers and 23 % hazardous, harmful or dependent alcohol users, with 10% displaying conjoint problem drinking and tobacco smoking.[5]

Both HIV-positive and HIV-negative TB patients will be enrolled. Participants will be enrolled consecutively in each clinic until the required sample size has been reached. Eligible patients must be in possession of a functioning cell phone Children, patients with extrapulmonary TB and those too ill to be interviewed will be excluded from the study.

Intervention: Participants in the interventions clinics will receive the PROLIFE brief MI intervention based on the Information-Motivation-Behavioural skill theory. In the initial MI session at the start of TB treatment the counsellor will establish rapport and the participant's tobacco smoking, problem drinking and other potential obstacles and facilitators for treatment adherence or initiation (both TB and ART treatment) will be determined. This first session will be concluded with agenda setting for the problem identified by the participant as the most salient. This could be a plan either to quit tobacco smoking, reduce drinking or deal with other perceived obstacles relating to ART or TB treatment. As all TB patients are eligible for ART, for participants who are HIV-infected and not yet on ART, beliefs and attitudes regarding HIV-testing or ART will be explored to facilitate ART initiation and adherence." The second session will build on the previous one and deal with challenges relating to the previous agenda setting, but then move on to the next behavioural problem (T, A or TA) where applicable. The third session will deal with the last identified problem. These individual counseling sessions will be re-enforced with SMS-based reminders regarding information supporting tobacco cessation, alcohol use and treatment adherence. Text messages will be delivered twice a week over 12 weeks and pre-tested as outlined above..

Comparator: Participants in control group will receive the usual counselling and support as currently rendered by LHWs at the clinics ("usual care").

Measurements: At enrolment assessment will consist of an interviewer-administered questionnaire plus a patient record review for the clinical information. The following information will be collected from questionnaires: socio-economic and demographic status, mine work (mineral dust exposure), AUDIT score, current tobacco smoking and quit history. Clinical information will be obtained from clinical records: first episode versus previous TB; site of TB; Gene expert, sputum and culture results at baseline; sputum conversion during the course of treatment, HIV-status, and ART information; diabetes and other co-morbidities such as pneumoconiosis.

The primary outcome will be the TB treatment success rate at 6 months follow-up. This outcome will be measured using the routinely collected programmatic TB treatment outcomes as defined by the WHO and adopted in South Africa[1]: successful treatment (cured or treatment completed), failed, died, acquired drug resistance, lost to follow-up/ "default", not evaluated. The term "default" will be replaced with the term lost to follow-up to reduce the use of blaming patient language.[40] Individual TB treatment records will be used as the primary source of information complemented with information from the TB register when individual information is missing. Attempts will be made to verify the information of patients classified as "default" or who are lost to follow-up by performing home visits or cross-referencing against home affairs records.

Secondary outcomes at 6 months follow-up: Sputum conversion at the end of treatment (measured by negative culture in the group of participants who had bacteriology confirmed PTB at baseline, i.e. cure rates in intervention group vs. control group for participants who initially had

sputum positive PTB); biochemically verified (exhaled Carbon Monoxide < 10 ppm) tobacco cessation, using the Russell Standards for tobacco cessation trials [41]; % reduction in harmful or hazardous drinking (measured with changes in the AUDIT score); TB drug and ART adherence (measured by self-report using the modified ACTG questionnaire)[42] and proportion of HIV-positive participants on ART. *Secondary outcomes at 3 months follow-up:* biochemically verified tobacco cessation; reduction in harmful or hazardous drinking; TB drug and ART adherence; proportion of HIV-positive participants on ART.

Sample size and statistical analysis: Based on an estimated 10% difference in TB treatment outcomes between intervention and control clinics using a success rates at national level for 2013 (86% vs. 76%), 80% power, 25% attrition and an intracluster correlation coefficient of 0.025 (estimate based on the ICC of a study in clinics in the Free State[44]) we will need to enrol approximately 960 participants or an average of 24 per clinic.

The statistical packages STATA and R will be used to carry out the analyses. After the appropriate descriptive analysis, the primary analysis will be conducted on an intention-to-treat basis and adjusted for the clustered design. Similar analyses will be carried out for the secondary outcomes with appropriate regression techniques. We will also adjust for baseline characteristics and other covariates. In case of missing data, we will employ a number of methods including multiple imputations to assess the sensitivity of the results. Statistical uncertainty about cost-effectiveness will be assessed with cost effectiveness uncertainty curves, accounting for the cluster randomized design.[45] Reporting of results will follow the CONSORT statement guidelines (http://www.consort-statement.org/).

Goal 3. To estimate the cost-effectiveness of the PROLIFE intervention

We will calculate the costs of both the PROLIFE counselling package and usual care, and also collect costs of wider use of health care such as physician and hospital visits by patients. Costs and outcome data will be combined to estimate the incremental cost per successfully treated case of TB. Comparing the incremental cost-effectiveness with the lifetime costs of TB care we will assess the potential for the intervention to save health care costs in the long term.

Goal 4. To conduct process evaluation relating to the design and delivery of the PROLIFE intervention programme

We will observe MI sessions during the piloting phase as outlined in goal 1 and evaluate intervention fidelity using an adapted MITI tool[39]. Patients will be interviewed after the first MI session and at the 3 month follow-up to determine the type of MI received and satisfaction with MI. LHWs will record MI sessions delivered on a standardised record-keeping tool.

Goal 5. To identify the key barriers and facilitators affecting the implementation of the PROLIFE model and propose a wider implementation plan

Focus group discussions and semi-structured interviews will be conducted with LHWs and health care managers, respectively. These will explore perceptions of the likely obstacles and potential opportunities for wider implementation of PROLIFE. The LHWs and managers will be purposively sampled based on the enthusiasm and success and lack of enthusiasm and success in implementing of PROLIFE during the trial. The findings of these two activities will be presented to policy makers, donors, and respective civil society organisations in a final 'Way Forward' workshop. The finalised implementation plan will also be presented as a toolkit.

6. Detailed Research objectives and activities by research goal

2.4.1 Goals, objectives and activities

Goal 1. To develop the PROLIFE model consisting of brief MI augmented with text messaging for promoting improved PTB outcomes through the Tobacco-Alcohol-TB treatment and ART package	
Objectives	**Activities**
To develop a context-adapted MI-based training package and manual	- Perform literature review - Develop the contents of the manual and the assessment tools through an expert panel workshop - Design user-friendly manual - Translate the manual - Print the manual
To train LHWs and to evaluate the training programme before and after	- Obtain ethics permission for the formative phase - Identify suitable LHWs - Determine pre-training knowledge on problem drinking, tobacco smoking and factors influencing treatment adherence (written test) in a workshop - Train LHWS in problem drinking, tobacco cessation and interventions for TB Rx and ART adherence (2 days) - Train LHWS in MI techniques (3 days) - Determine post-training knowledge on problem drinking, tobacco smoking and factors influencing treatment adherence (written test) -
To determine the barriers and facilitators for the PROLIFE model	- Develop the protocol for the focus group discussions including the interview guide (explore barriers and facilitators to adherence relating to Information, Motivation, Behavioural Skills, moderating factors). - Hold the focus group discussions - Transcribe and translate the focus group discussions - Perform thematic analysis - Adapt the MI and SMS content to focus group results
To assess organisational capacity and readiness for change	- Develop the protocol for semi-structured interviews - Obtain ethical approval - Hold semi-strucured interview with health care providers and managers: o 3 district TB managers o 6 clinic managers (2 per study site) o 3 provincial TB managers (FS, NW and Gauteng) o 1 national TB manager - Transcribe the interviews - Perform thematic analysis - Adapt the intervention to the findings of the semi-structured interviews
To develop and test a mobile phone messaging system to augment the effect of the intervention	- Perform Literature review of existing messages - Develop the SMS messages (expert panel workshop) - Culturally adapt and format the messages - Prioritise the message delivery order - Hold a technical protocol workshop and develop the SOPS for staff and materials for patients - Train the 26 LHCWs of the intervention clinics in the use of the SMS-messaging system - Pilot the SMS messaging system on a sample of TB patients who smoke and /or drink (3 patients per trained LHW)

To pilot the brief MI and SMS package with real-life TB patients	- Identify suitable piloting clinics (3 per district)
	- Pilot the MI counselling with a sample of TB patients who smoke and /or drink (3 patients per trained LHW, 3 counselling sessions per patient (month 0, 1 and 2)
	- Pilot the SMS messaging system with the same TB patients who smoke and /or drink (3x8 messages over 3 months)
	- Evaluate intervention fidelity of MI sessions
	- Evaluate positive and negative experiences with MI and SMS-system (TB patient and LHW exit semi-structured interview)
Goal 2. To estimate the effectiveness of the PROLIFE intervention delivered by LHWs in improving PTB treatment outcomes versus usual care	
- To estimate the effectiveness of the PROLIFE intervention on increasing successful PTB treatment outcomes at 6 months follow-up. - To estimate the effectiveness of the PROLIFE intervention on sustained tobacco abstinence - To estimate the effectiveness of the PROLIFE intervention on reducing problem drinking - To estimate the effectiveness of the PROLIFE intervention on self-reported TB drug adherence - To estimate the effectiveness of the PROLIFE intervention on ART initiation or adherence	- Develop a detailed research protocol with baseline, 3 month and 6 month assessment tools - Approval of study extension by UK and SMU ethics committee - Develop the data management platform and train 40 fieldworkers on data collection - Hold a 2 day refresher MI workshop for LHCWs of intervention clinic - Enrol TB Patient (6 months) and follow them up for 9 months) - Perform data cleaning and analysis - Write research report and publications
Goal 3. To estimate the cost-effectiveness of the PROLIFE model	
- To assess the costs of delivering the PROLIFE model - To assess the cost-effectiveness of the PROLIFE model	- Estimate the costs of delivery of the PROLIFE intervention vs. routine care - Combine costs and outcomes to determine the incremental cost-effectiveness
Goal 4. To conduct process evaluation relating to the design and delivery of the PROLIFE model	
- To assess the intervention fidelity of the MI counselling - To determine the number and type of counselling delivered (T, A, AT)	- Assess MI fidelity during piloting, using an adapted MITI tool [39] - Hold exit interviews with participants - Monitor interventions delivered by LHWs through record keeping
Goal 5. To identify the **key barriers and facilitators** affecting the implementation of the PROLIFE model and propose a **wider implementation**	
- To explore perceptions of the likely obstacles and potential opportunities for wider implementation of PROLIFE.	- Hold focus groups with LHWs - Hold semi-structured interviews with health care managers - Way forward workshop

7. Ethical considerations

Ethics and management approvals

Ethics approval will be sought from the Ethics committees of the University of Pretoria, Sefako Makgatho University, the Medical Research Council, the University of the Free State, the University of Witwatersrand and the University of York.

Managerial approval will be obtained from the provincial and/or district managers (as required) to conduct the study at clinics in Bojanala district (North West Province), Lejweleputswa district (Free State province) and Sedibeng district (Gauteng province). (Appendix 10)

Respect for autonomy and confidentiality

For the focus group discussions and semi-structured interviews, informed consent will be obtained from each participant before the actual group discussions or interviews (see PIC 1 and 2).
Similarly individual consent will be obtained for the before-after training of LHWs (PIC 3).

For the field evaluation of the MI intervention with TB patients, consent will be obtained from individual patients and from LHWs to administer questionnaires about their satisfaction with the SMS and MI package and for the audio-taping and evaluation of the MI sessions (PIC 4 and PIC5).

The identity of focus group participants and semi-structured interview participants will be protected. Their names will be removed from any records before analysing the data.

The before–after training evaluation forms will have unique study numbers. Personal identifiers of the study participants will not be written on the forms. Similarly, the audio-files of the pilot MI counselling sessions will be labelled with study numbers allocated to LHWS and not contain any names. This will ensure anonymity for the data analysis. The screening forms for the identification of eligible TB patients for the piloting session will contain the contact details and names of the TB patients as they may need to be contacted for follow-up MI sessions. However personal identifiers will be removed once data are entered for data analysis. All questionnaires will be stored safely in locked cabinets and offices. Electronic data will be password protected.

Participants will be allowed to withdraw from the study at any time without giving a reason for their withdrawal.

Beneficence

Focus group participants and managers may not directly benefit from participating in the discussions and interviews but their contributions will be crucial in guiding the design of the intervention package and the cluster RCT.

LHWs will benefit from the training in MI counselling and alcohol and tobacco use. This will benefit future patients who are counselled by these LHCWs and help to improve the intervention for future use in the cluster randomised controlled trial.

Individual TB patients enrolled in the study will benefit from the MI counselling and SMS messages received. These interventions will help them to quit smoking, reduce harmful drinking and find ways to increase TB treatment and ART adherence and may ultimately improve TB treatment outcomes and have other long-term positive health effects.

Non-maleficence

The project is unlikely to be directly harmful to TB patients participating in the pilot with the exception of inconvenience in terms of time spent on the counselling session.

Reimbursement for expenses incurred by participants

Focus group participants will be reimbursed for travel costs and be provided with drinks and snacks after the focus group session.

LHWs will be compensated for travel costs relating to the training and will receive R 500/day stipend for the 5 training days.

No reimbursement will be provided to interviewees of the semi-structured interviews. The interviewer will travel to the interviewee at a time and place convenient for the interviewee.

TB patients participating in the study will receive R60 travel and other expenses reimbursement for each MI counselling session and follow-up visit related to the study.

8. Time line: Milestones and Deliverables (3 –year project)

***A detailed project timeline for goal 1 is attached as appendix* 2.**

Key Tasks	**Duration (Start-End Date)**												**Deliverable(s)***
Milestone 1: Complete the formative, developmental phase													
	Feb-Apr 2016	**May-Jul 2016**	**Aug-Oct 2016**	**Nov 2016-Jan 2017**	**Feb-Apr 2017**	**May-Jul 2017**	**Aug-Oct 2017**	**Nov 2017-Jan 2018**	**Feb-Apr 2018**	**May-Jul 2018**	**Aug-Oct 2018**	**Nov 2018-Jan 2019**	
Development of context-adapted MI-based training package and manual													Training package delivered
Evaluation of the training programme before and after													LHWs trained and before-after training results analysed and acted upon
Focus groups to evaluate the barriers and facilitators for the project model													Barriers and facilitators for the project model identified
Assessment of organizational capacity and readiness for change													Organisational capacity established
Development and testing of mobile phone messaging system													Mobile phone messaging package developed
Pilot the SMS and MI package with TB patients													
Milestone 2: Complete the effectiveness study													
	Feb-Apr 2016	**May-Jul 2016**	**Aug-Oct 2016**	**Nov 2016-Jan 2017**	**Feb-Apr 2017**	**May-Jul 2017**	**Aug-Oct 2017**	**Nov 2017-Jan 2018**	**Feb-Apr 2018**	**May-Jul 2018**	**Aug-Oct 2018**	**Nov 2018-Jan 2019**	
Develop research protocol													
Approval by relevant ethics committees													

Piloting including piloting of data management system													
Data collection (cluster RCT +process evaluation)													
Data analysis and write-up													Effectiveness of intervention established Process evaluation completed
Milestone 3: Complete cost-effectiveness study													
	Feb-Apr 2016	**May-Jul 2016**	**Aug-Oct 2016**	**Nov 2016-Jan 2017**	**Feb-Apr 2017**	**May-Jul 2017**	**Aug-Oct 2017**	**Nov 2017-Jan 2018**	**Feb-Apr 2018**	**May-Jul 2018**	**Aug-Oct 2018**	**Nov 2018-Jan 2019**	
Intervention cost estimation													
Cost-effectiveness estimation													Cost-effectiveness determined
Milestone 4: Sustainable Implementation and scaling-up of intervention plan													
	Feb-Apr 2016	**May-Jul 2016**	**Aug-Oct 2016**	**Nov 2016-Jan 2017**	**Feb-Apr 2017**	**May-Jul 2017**	**Aug-Oct 2017**	**Nov 2017-Jan 2018**	**Feb-Apr 2018**	**May-Jul 2018**	**Aug-Oct 2018**	**Nov 2018-Jan 2019**	
Focus groups and semi-structured interviews with LHWs and managers													
Way forward workshop													Finalised implementation plan and tool kit

*Please include scientific/product deliverables here and not publications, presentations or personnel capacity development

9. Budget and funding

This project is funded by the SA-Medical Research/Newton Foundation Grant on TB control implementation science. (UK/South Africa Newton Fund RFA: TB control implementation science (MRC-RFA-02: TB -05-2015)

Summary Budget

SA Costs

BUDGET ITEMS PERSONNEL COSTS	Year 1	Year 2	Year 3
PI 1	R 974 010.00	R 3 110 000.00	R 2 115 170.00
PI 3	R 0.00	R 0.00	R 0.00
Total - Project Personnel Costs	**R 974 010.00**	**R 3 110 000.00**	**R 2 115 170.00**
LABORATORY COSTS			
PI 1	R 0.00	R 0.00	R 0.00
PI 3	R 0.00	R 0.00	R 0.00
Total - Project Laboratory Costs	**R 0.00**	**R 0.00**	**R 0.00**
TRAVEL COSTS			
PI 1	R 368 840.00	R 276 120.00	R 142 100.00
PI 3	R 0.00	R 0.00	R 0.00
Total - Project Travel Costs	**R 368 840.00**	**R 276 120.00**	**R 142 100.00**
OTHER DIRECT COSTS:			
PI 1	R 567 459.16	R 827 162.50	R 262 749.17
PI 3	R 0.00	R 0.00	R 0.00
Total - Other Direct Project Costs	**R 567 459.16**	**R 827 162.50**	**R 262 749.17**
EQUIPMENT / CAPITAL ITEMS			
PI 1	R 6 000.00	R 280 000.00	R 0.00
PI 3	R 0.00	R 0.00	R 0.00
Total - Project Capital Costs	**R 6 000.00**	**R 280 000.00**	**R 0.00**
TOTAL: DIRECT COSTS	**R 1 916 309.16**	**R 4 493 282.50**	**R 2 520 019.17**
TOTAL: INDIRECT COST (INSTITUTIONAL LEVY)	R 95 515.46	R 210 664.13	R 126 000.96
TOTAL COST PER ANNUM	**R 2 011 824.62**	**R 4 703 946.63**	**R 2 646 020.13**
	TOTAL COST		**R 9 361 791.37**

INFLATION ADJUSTED COST	**R 2 011 824.62**	**R 4 986 183.42**	**R 2 804 781.33**
	TOTAL COST		**R 9 802 789.37**
TOTAL COST PER ANNUM (£)	*£11 201.03*	*£ 27 761.07*	*£ 15 615.90*
			£ 54 578.01

UK Costs				
	Year 1	**Year 2**	**Year 3**	**Total**
DA - Estate Costs	R 73 485.34	R 73 485.34	R 73 485	R 220 456.01
DA - Other Directly Allocated	R 0	R 0	R 0	R 0
DA - Investigators	R 196 302.40	R 233 053.26	R 236 028.41	R 665 384.06
DI - Equipment	R 0	R 0	R 0	R 0
DI - Other Costs	R 62 289.60	R 31 144.80	R 95 073.60	R 188 508.00
DI - Staff	R 152 003.02	R 240 577.19	R 244 281.78	R 636 861.98
DI - T&S	R 0	R 0	R 0	R 0
Indirect - Indirect Costs	R 325 430.38	R 325 430.38	R 325 430.38	R 976 291.13
Exception - Equipment	R 0	R 0	R 0	R 0
Exception - Other Costs	R 0	R 0	R 0	R 0
Exception - Staff	R 0	R 0	R 0	R 0
Exception - T&S	R 0	R 0	R 0	R 0
UK COSTS SUMMARY ZAR	R 809 510.72	R 903 690.96	R 974 299.50	R 2 687 501.18
Inflation adjusted costs	R 809 510.72	R 914 987.10	R 986 478.24	R 2 710 976.06
UK COSTS SUMMARY £	*£39 507.60*	*£44 104.00*	*£47 550.00*	*£131 161.60*
Inflation adjusted costs	£39 507.60	£44 655.30	£48 144.38	£132 307.28

Total Combined UK & SA Costs				
	Y1	**Y2**	**Y3**	**Total**
ZAR	R 2 821 335.34	R 5 901 170.52	R 3 791 259.58	R 12 513 765.44
GBP	£50 708.63	£72 416.37	£63 760.28	£186 885.29

10. Overview of the applicant's own research relevant to the project

OAY has designed and led research in monitoring tobacco control policy implementation in several African countries and more recently pioneered research in using the MI technique delivered by LHWs to promote smoking cessation within TB treatment settings together with one of the co-investigators of this grant - GML. This work, although relatively recent, has found its way into a recently published Cochrane review and a monograph on cost-effectiveness of various smoking cessation interventions. Having trained over 600 health care professionals in tobacco use cessation using the brief MI technique across 12 countries in Africa, he has been able to design and deliver a cost-effective approach to training different cadres of health workers and established a network of regional, national and international collaborators, including working with KS in putting together a recent review on the subject and presenting a symposia at the World Congress earlier this year. This seminal work on promoting smoking cessation in TB patients follows on research he has conducted in one of the proposed research sites to understand why physicians do not actively intervene and patients' own level of comfort in having such an intervention to support smoking cessation. He has secured a research income of approximately 3 million US dollars as principal investigator through competitive research and capacity-building grants from a range of funders. His scientific contributions have so far led to 75 scientific publications in peer-reviewed journals, two book chapters and technical reports. He has been serving on the WHO scientific group on tobacco regulation (TobReg) since 2008 and he is a well-recognized regional and national leader in the field of smoking cessation.

In addition to his scientific standing acknowledged with a C2-rating by the National Research Foundation, OAY is currently an Executive Dean at his University, having previously served as the Chief Executive Office of a district hospital and successfully led a number of international and regional collaborative projects. He therefore has the requisite leadership and administrative capabilities that will serve to manage the current project successfully.

The scientific standing of OAY as a health promotion specialist is complimented by the significant scientific standing of his Co-PI (KS) and other senior scientists in the group in the field of TB and implementation science (OMB, SP, and NM). OMB conducted several pragmatic randomised controlled trials on HIV/AIDS/ART and tuberculosis care in South African primary care clinics and has an excellent grounding in health services research, epidemiology and biostatistics. NM has extensive research experience w.r.t motivational interviewing and the links between problem drinking and HIV. GML's research expertise is in the field tobacco cessation in TB patients, TB and HIV integration and the links between tobacco, alcohol, HIV and TB. This project is thus founded on our existing collaborations.

KS conducted a systematic review on the effectiveness of clinical, laboratory and health systems tools, in improving smear-negative TB diagnosis (published in Lancet Infections Diseases). Subsequently, he developed and evaluated clinical, laboratory and health systems interventions for improving smear-negative TB diagnosis, as follows: (a) Clinical – A new clinical algorithm to diagnose smear-negative TB and assessment of its sensitivity and specificity. The study showed that the algorithm could improve smear negative TB diagnosis. (b) Laboratory – A literature review on laboratory techniques to enhance sputum microscopy yield and evaluation of sputum concentration. (c) Health Systems – Evaluating the effect of clinical audit in improving smear-negative TB diagnosis in a multi-country study. The study found that clinical audit, if integrated within local TB control, could improve the quality of TB care, in general and TB diagnosis in particular. He developed clinical guidelines for smear-negative TB for the National TB Programme, Pakistan. His work was used by WHO in developing its own international guidelines for diagnosing smear negative TB and was also cited in the International Standards for TB Care - the 'gold standard' for TB care worldwide. His systematic review on smear negative TB, cited 265 times, remains one the two most cited reviews on this topic.

Supported by an IDRC grant, KS conducted the 'Action to Stop Smoking in Suspected Tuberculosis' (ASSIST) study in Pakistan. This was the first ever smoking cessation randomised controlled trial (RCT) in TB. The study found that behavioural support (with or without bupropion) was seven to eight times more likely to be successful than usual care in achieving smoking abstinence. He also found that behavioural support would only cost as little as 10 USD per quit.

11. Available Infrastructure

The University of York team is embedded in the Department of Health Sciences who research in public health and health services. The Department employs over 130 active researchers, who work across five themes: Public Health and Society; Trials and Statistics; Cancer Epidemiology and Cardio-Vascular Health; Mental Health and Addiction; and Health Services and Policy. The proposed work, therefore, will benefit from being located in a dynamic research culture, which is further support by staff development and research career initiatives. The Department also has its own research management unit, and marketing and communication team. The randomised controlled trial proposed in this application will be supported by a statistician from the York Trials Unit. The Unit provides a number of services including study design, randomisation, trial coordination, data management, statistics, economic evaluation and outcomes.

The existing infrastructure at SMU in the form of the Mecru Clinical Research Unit would be adequate to support the proposed research. The Family Medicine Department under the guidance of Prof J. Tumbo at the SMU manages the Bojanala District as a clinical training platform for the medical students of the SMU – the largest standalone Health Sciences University in Africa. There is long standing relationship between the provincial government and the University and several clinical trials have been conducted by the Mecru research staff that might be involved with data management for this current project. The SMU strongly supports the development of new research programmes such as this as it complements existing multicentre collaborative clinical trials on HIV vaccines, microbicides, a TB-ART study and a study on a new drug for the treatment of MDR-TB (NeXT study) funded by the SA Medical Research council.

The Free State leg of the study will be coordinated by the Centre for Health Systems Research and Development (CHSRD) which has been in existence for 21 years. At present the CHSRD has five researchers, a research administrator and a secretary/financial officer. Over the years the Centre has established a network of available fieldworkers – many who have participated in various health care facility, patient and household surveys mainly relating to HIV and TB research. The CHSRD works collaboratively with the Free State DoH, involving them from proposal development to data dissemination. Our partners at Wits also have access to TB treatment facilities and patients and the provincial government leadership through existing research programmes (see attached letters of support from National Department of Health and Provincial programme managers).

12. Project Significance

Expected Outputs, Outcomes and Impact

The research proposed is informed by our previous published work thus increasing the feasibility of successfully conducting this project. Research results will not only be published in international indexed journals, but will be disseminated to managers of the provincial and national departments of health. Furthermore, the provincial and national Departments of Health would be involved in the design and final evaluation of the project so as to assure their ownership and sustainability and scaling the programme beyond the life of the current project.

At least two PhD students and two master's students will be involved in the project and be supervised and guided to write up a thesis or dissertation. The additional international experience in implementation research and economic evaluation brought to the team by our UK partners provides opportunities to capacity strengthening both at an institutional and individual level. Therefore, in line with the aim of this RFA, the current collaborative project has the potential to expand implementation science research that will support the national TB control programme by increasing the capacity to conduct large, multinational projects. Furthermore, considering that the South African primary applicant institution and the three proposed study sites have been previously under-resourced, the current project would provide further development of an appropriate infrastructure to support implementation research and provide access to key populations for research, namely districts with a high TB burden in mining areas.

Scientific significance (locally and globally)

South Africa is ranked fourth among 22 high burden countries in the world, but the second highest prevalence of TB per capita with 998 cases per 100,000 populations with at least 60% co-infected with HIV. TB is currently the leading cause of death in South Africa with no significant increase in treatment success in recent years. Among others, inadequate provider-patient communication has been associated with treatment failures. Yet, there are no widely disseminated facility-based programmes aimed at optimizing patient-provider communication within TB control programmes. The MI technique used in PROLIFE is a well-studied patient-centered communication style that is likely to improve the practice of effective patient-provider communication. Furthermore, the information of the kind sought from this project may be useful in improving the design and dissemination of appropriate and cost-effective facility-based tobacco and harmful alcohol use cessation programme that may impact not only on curbing the rising burden of non-communicable diseases and the prevention of TB transmission, but will also impact on TB and ART treatment adherence and by implication improve TB treatment outcomes and save lives. The current project therefore also seeks to shift clinical practice paradigm by utilizing lay health workers to deliver life-saving intervention for TB patients. The research proposed therefore responds to post-2015 sustainable development goal (SDG) 3, i.e. ensuring healthy lives and promoting well-being.

Potential Impact

The proposed model of care will integrate locally adapted MI delivered by LHWs, with innovative low cost SMS technology to control TB and thus ensure implementation in a sustainable and scalable manner.

PROLIFE will adopt a robust range of realistic, clinical, patient, economic and process outcome measures to evaluate this multifaceted model of care, resulting in a number of important short, medium and long term impacts in the area of TB control, as well as providing strategies for chronic disease control in South Africa.

The study will have a constructive impact as follows: (a) It will improve TB outcomes in South Africa - our study will be the first to assess and demonstrate the effect of modifying lifestyle risk factors on TB treatment outcomes. (b) It will improve the health of the very vulnerable - TB affects one of the most impoverished groups and smoking and alcohol misuse in such people has devastating health and economic consequences. If successful and taken up, our intervention could lead to a reduction in the burden of disease in extremely impoverished people and thus reduce health inequality. (c) Knowledge translation and scaling up into policy and practice - Our research is grounded within implementation science, attempting to answer questions that are highly relevant to programme managers. Being a research partner, the findings will be owned by the TB programme in South Africa enabling the adoption, scaling up and sustainability of such intervention. (d) A new model of programme implementation: South Africa lacks the infrastructure to offer specialist smoking cessation and alcohol services at a scale. In this study, we will develop knowledge on how best to ‘piggy back’ such intervention to an existing programme.

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14. Appendices

1. Letter to the chairperson explaining request for ethics permission for year 1 in the context of larger project.
2. Detailed time frame for Goal 1 (year 1).
3. Letter from the MRC indicating grant approval.
4. Focus group discussion guides and PIC 1.
5. Semi-structured interview guide and PIC 2.
6. Before-after training evaluation instrument and PIC 3.
7. Screening instrument for TB patients' eligibility and PIC 4.
8. Semi-structured questionnaire for LHWs re the challenges experienced and satisfaction with the counselling and SMS-package and PIC 5.
9. Semi-structured questionnaires for patients enrolled in piloting projects, re the challenges experienced and the satisfaction with the counselling and SMS messages and PIC 6.
10. Letters to management and provincial committees requesting permission to execute study at the 3 study districts + all required forms in terms of the committee.
11. Other required information

    Helsinki declaration

    Storage of records for 15 years

    CVs of researchers