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Effect of a brief motivational interview and text message intervention targeting tobacco smoking, alcohol use, and medication adherence to improve tuberculosis treatment outcomes in adult patients with tuberculosis: a multicentre, randomised controlled trial of the ProLife programme in South Africa

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ABSTRACT

Objectives: To investigate the effectiveness of a complex behavioural intervention, ProLife, on tuberculosis (TB) treatment success, medication adherence, alcohol use and tobacco smoking.

Design: Multicentre, individual, randomised controlled trial where participants were assigned (1:1) to the ProLife intervention or usual care.

Setting: 27 primary care clinics in South Africa.

Participants: 574 adults starting treatment for drug-sensitive pulmonary TB who smoked tobacco or reported harmful/hazardous alcohol use.

Interventions: The intervention, delivered by lay health workers (LHWs), consisted of 3 brief motivational interviewing (MI) sessions, augmented with Short Message Service (SMS) messages, targeting medication adherence, alcohol use and tobacco smoking.

Outcome measures: The primary outcome was successful versus unsuccessful TB treatment at 6 to 9 months, from TB records. Secondary outcomes were biochemically confirmed sustained smoking cessation, reduction in the Alcohol Use Disorder Identification Test (AUDIT) score, improved TB and antiretroviral treatment (ART) adherence and ART initiation, each measured at 3 and 6 months by questionnaires; and cure rates in patients who had bacteriology-confirmed TB at baseline, from TB records.

Results: Between 15 November 2018 and 31 August 2019, 574 participants were randomised to receive either the intervention (n=283) or usual care (n=291). TB treatment success rates did not differ significantly between intervention (67.8%) and control (70.1%; OR=0.9 (95% CI: 0.64,1.27)). There was no evidence of an effect at 3- and 6-months respectively on continuous smoking abstinence (OR=0.65 (95% CI: 0.37,1.14); OR=0.76 (95% CI: 0.35,1.63)), TB medication adherence (OR=1.22 (95%CI: 0.52,2.87); OR=0.89 (95%CI: 0.26,3.07)), taking ART (OR=0.79 (0.38,1.65), OR=2.05 (0.80,5.27)) or AUDIT scores (mean score difference 0.55 (95% CI: -1.01,2.11); -0.04 (95% CI: -2,1.91); and adjusting for baseline values. Cure rates were not significantly higher (OR=1.16 (0.83,1.63)).

Conclusions: Simultaneous targeting of multiple health risk behaviours with MI and SMS using LHWs may not be an effective approach to improve TB outcomes.

Trial registration: ISRCTN62728852, Registered on 13th April 2018.

Key words: Tuberculosis, smoking, alcohol, motivational interviewing, mHealth, anti-retroviral therapy, adherence

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The use of motivational interviewing combined with Short Text Messaging to address the effect of multiple risk behaviours (smoking, drinking and poor adherence) on tuberculosis treatment outcomes is a novel and much needed intervention.
- Our study design was strong: this was a multi-site individually randomised controlled trial with a large sample size and a high follow up rate for the primary outcome.
- We used validated measurement tools; furthermore, data analysis and primary outcome assessment were blinded, thereby limiting measurement bias.
- However, the study was underpowered for secondary outcomes, and low intervention uptake may have diluted any potential intervention effects.

INTRODUCTION

Tuberculosis (TB) is among the most common chronic infectious diseases in the world today. In 2019, 1.4 million deaths worldwide were attributed to TB, and the majority of these occurred in low-income and middle-income countries (LMICs).(1) South Africa not only has one of the highest TB burdens in the world; it is faced with high TB treatment interruption and loss to follow-up rates. It also has a high prevalence of human immunodeficiency virus (HIV) co-infection in patients with TB and a relatively high mortality in these co-infected patients.(1) Studies of interventions to advance the goal of ending the TB epidemic and improving treatment outcomes are therefore research priorities in South Africa and other LMICs.(2)

Mortality and morbidity from TB is strongly associated with health risk behaviours, particularly smoking and hazardous or harmful alcohol use, both of which are prevalent and often co-occur in patients with TB.(3–10) Strategies are also required to improve TB medication adherence in patients with TB and adherence to TB medication and anti-retroviral therapy (ART) in patients co-infected with TB and HIV, both of which may be negatively influenced by excessive alcohol use.(1) There is very limited research on how to concurrently tackle these three risk behaviours - namely smoking, harmful alcohol use and poor medication adherence - in patients with TB, particularly in LMICs.

Motivational Interviewing (MI) has been shown to support reduced drinking, smoking cessation in TB patients and TB treatment and/or antiretroviral therapy (ART) medication adherence.(11–13) MI interventions can be effectively delivered by lay health workers (LHWs).(14) The more widespread use of LHWs and the increased use of mobile health (mHealth) digital technologies represent promising ways to increase the scalability of MI interventions. Indeed, the World Health Organisation (WHO) has called for researchers to capitalise on advances in mobile phone technology, network coverage and the increased use of common and widely available digital technologies (including the mobile phone short message service (SMS)) to improve TB care.(15) There is evidence that mHealth technologies can have modest beneficial effects on a range of health outcomes, including medication adherence.(16,17) Mobile phone messaging also shows a modest effect in improving TB treatment success rates.(18,19) The evidence is however stronger for two-way messaging and interactive systems for which smart phones are required.(18) These are often not available to patients with TB in Africa.(20)

A limitation of existing MI and mHealth interventions is that they have been studied in the context of modifying a single lifestyle factor. Integrated interventions are likely to be better accepted and more effective than multiple interventions targeting different health risk factors.(21,22) In the case of TB,

there is a need for an intervention that has the flexibility to target multiple lifestyle factors as appropriate and in line with patient preferences. This could be achieved through increased integration of TB and non-communicable disease services.(23)

Recent re-engineering of primary health care in South Africa has seen the introduction of municipal ward-based primary healthcare outreach teams of community health workers (CHWS). CHWs work in an integrated, team-based manner, supported by nurses, and take responsibility for health education and promotion, counselling and support for a range of health conditions.(24,25) Task shifting in this context has been shown to improve population health in LMICs (26) and these teams can be trained and supported to take responsibility for TB/HIV care.(27) Integrated interventions could be implemented within this framework in a feasible and scalable way to improve outcomes for patients with TB across South Africa and beyond.

Building on previous successes with MI and mHealth interventions, we developed a complex behavioural intervention (ProLife) comprising MI-based counselling and SMS, targeting three lifestyle risk behaviours for poor TB outcomes (smoking, hazardous/harmful alcohol consumption and poor medication adherence), and delivered by LHWs. We then conducted a randomised controlled trial (RCT) to assess the effectiveness of the ProLife intervention on improving TB treatment outcomes, smoking abstinence, reducing alcohol consumption and improving adherence to TB and ART medication compared to usual care. The cost-effectiveness of the intervention was also assessed but only the costing results will be presented in this paper.

METHODS

Study design and participants

This was a prospective, two-arm, multicentre, individual RCT, which took place across 27 primary care clinics in 3 districts in South Africa (Lejweleputswa in the Free State province; Bojanala in the North West province; and Sedibeng in Gauteng province). Adult patients (18 years or older) were eligible for the study if they had drug-sensitive Pulmonary TB (PTB), and were initiating TB treatment or had been on TB treatment for less than a month for this treatment episode (both “new” and “retreatment patients”). They had to be tobacco smokers (defined as smoking daily or non-daily in the last four weeks on the Global Adult Tobacco Survey questionnaire)(28) and/or hazardous/harmful drinkers who were not alcohol dependent (Alcohol Use Disorders Identification Test (AUDIT) score ≥ 8 for men or ≥ 7 for women but <20).(29) They also had to have access to a

mobile phone and understand one of the 4 languages used for the trial (English, IsiZulu, SeSotho and Setswana). Potential participants were recruited consecutively at the participating clinics between 15 November 2018 and 31 August 2019. Trained field workers identified those interested in the study and screened them for eligibility. If eligible and willing to be enrolled into the trial, written informed consent was obtained. The RCT received ethics approval from the Research Ethics Committees of the five participating research institutions and the trial protocol was previously published.(30)

Randomisation and blinding

Patients were centrally randomised (1:1) to the ProLife intervention or control group using a randomised sequence generator by the trial statistician (MK) who was blind to the arm allocation. We used block randomisation with varying block sizes stratified by clinic so as to achieve equal numbers in intervention and control groups within each clinic. Fieldworkers used sequentially numbered, sealed, opaque envelopes to allocate participants to intervention or control. ProLife involved a complex behavioural intervention therefore LHWs and participants could not be blinded to the intervention. However, the determination of the primary outcome was done by the TB nurses who were blinded to the intervention status of the participants, based on routinely collected data. The statistician (MK) was blinded to the intervention or control arm allocation of participants during the analysis.

Intervention and procedures

The ProLife intervention was developed based on a conceptual framework, following a review of pre-existing evidence.(31) This framework assumed that smoking cessation, reducing harmful alcohol use and improved adherence to TB and HIV treatment would result in improved TB treatment outcomes.(30) The intervention consisted of 3 brief MI counselling sessions, lasting 15-20 minutes, one month apart, delivered by trained LHWs at their TB clinic. The first MI session took place immediately or shortly after the randomisation and involved prioritisation and agenda setting, wherein the participant determined which factor should be prioritised (either a plan to quit tobacco smoking, or reduce or quit drinking, or deal with barriers relating to ART or TB medication adherence). The second and third sessions built on the previous one until all relevant behavioural problems had been addressed. These sessions were reinforced with follow-up SMS text messages, twice a week over 12 weeks.(30) Study patients received 10 TB-related messages followed by seven alcohol reduction- and/or seven smoking cessation-related messages, as appropriate. Messages were aimed at giving information, and augmenting motivation or behavioural skills (we refer to the

feasibility paper for more details).(31) Applicable SMS-messages were automatically activated after the first MI had taken place. Thereafter remaining messages were delivered even if the participant did not attend the second or third MI session.

Participants randomised to the ProLife intervention also received the same "usual care" as those in the control group. The control group received the usual care and routine treatment and support offered to patients with TB in South Africa, which varies by district but includes: health education; dietetic input; social support; point of care biochemical testing; and HIV testing with pre- and post-test HIV test counselling.

Data were collected at baseline, 3- and 6-months and recorded by fieldworkers equipped with mobile phones with the ProLife mobile data collection application (built with CommCare)(32) installed. They used a standardised electronic case report form (CRF) and followed standard operating procedures (SOPs) to ensure quality. Details of data collection, protection and storage procedures have been reported elsewhere.(30)

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Outcomes

Primary Outcome

The primary outcome of TB treatment success at 6 to 9 months follow-up (depending on when it was recorded) was as per the WHO definitions adopted in South Africa,(10) that is, either successful treatment (cured or treatment completed) or failed treatment, death, acquired drug resistance, loss to follow-up (defined as treatment interruption of more than 2 months), or outcome not evaluated. It was measured using the routinely collected TB treatment outcomes in patients' individual files.

Secondary Outcomes

For those participants with bacteriologically confirmed PTB at baseline (either sputum acid fast bacilli (AFB) positive, culture positive or GeneXpert positive PTB), sputum conversion at the end of treatment ("cure rate") was measured as a secondary outcome.(10) Continuous smoking abstinence was assessed at 3- and 6-months follow-up in those participants who were current cigarette smokers

at baseline. It was defined as having quit smoking completely and a self-report of not smoking more than 5 cigarettes from the start of the study, in addition to a negative biochemical test (exhaled Carbon Monoxide (CO) < 7 ppm).(33,34) Changes in alcohol consumption were computed using the AUDIT questionnaire scores measured at 3- and 6-months follow-up in those participants who were hazardous/harmful drinkers at baseline.

HIV positive participants were asked about ART status at baseline, 3- and 6-months using standardised questions on the CRF and change in ART status as measured at the 2 follow-up times.

TB and ART medication adherence was measured using modified versions of the AIDS Clinical Trials Group Adherence Questionnaire, a validated tool for measuring adherence specifically to ART.(35) Adherence was measured using an adherence index calculated by the formula (using the 4-day recall): [Total number of doses taken/Total number of doses prescribed] x 100. Patients with at least 95% adherence were classed as having optimal adherence and those with less than 95% were classed as having low (or suboptimal) adherence. This was assessed at 3- and 6-months.

During COVID-19 lockdown (in the second term of 2020) we switched to telephonic follow-up of participants using a shortened questionnaire whereby only strictly needed information for the measurement of outcomes was inquired about.

Training and Intervention Fidelity Monitoring

The training and intervention fidelity monitoring is described in more detail in previous papers.(30,31) In brief, 18 LHWs, 3 district coordinators and 1 research assistant who focused on counselling supervision underwent MI training over 5 days. LHWs completed a post-session semi-structured form onto which they indicated the extent to which they implemented each element of MI, as well as their general qualitative impressions of that particular session. In addition, we assessed MI intervention fidelity based on ratings of the counsellors' recorded MI sessions, as described below and in footnotes to the relevant supplementary table. SMS-message delivery was also assessed.

Economic evaluation

The ProLife intervention costs consisted of the costs of training and the delivery of the ProLife intervention, including relevant personnel involvement (trainers and LHWs), materials used, travel, accommodation and refreshments, and digital infrastructure for the intervention. These were estimated based on research team records. Usual care costs consisted of TB medication costs, biochemical investigations, and ART costs if applicable. These were estimated based on information

obtained through routine records. The country specific version of Euroqol with 5 dimensions and 3 levels of response categories (EQ-5D-3L) for South Africa was administered to participants at baseline, 3- and 6-months follow-up to measure health-related quality of life.(36,37)

Statistical analysis

The sample size was estimated at 696 in total (348 participants per arm), to detect a 10% difference in TB treatment success rates (0.86 vs. 0.76) in the ProLife arm (intervention) vs. the control arm with 80% power, a significance level of 0.05 and 25% attrition rate. The assumed success rates in the control group were based on actual success rates in patients with TB in the studied provinces obtained from TB managers at the time of the grant application for this study.

We summarised baseline data descriptively by trial arm. For the primary outcome, we conducted statistical analysis on an intention-to-treat basis. We used binary logistic regression to compare the main outcome (TB treatment success rate) between the intervention and the usual care arm. Where treatment outcome data were missing, the outcome was coded as unsuccessful. TB treatment outcomes recorded by the TB nurse were taken on face value as inconsistencies in the dates of bacteriological results did not permit us to verify the correctness of the nurse assessment. We carried out similar statistical analyses for the secondary outcomes with appropriate regression techniques. For the reduction in harmful or hazardous drinking, we used linear regression to estimate the difference in total AUDIT score between control and intervention groups accounting for the baseline AUDIT score as covariate. Separate analyses at 3- and 6-months were performed.

For our main analyses we adjusted for baseline characteristics if these differed between trial arms at baseline. The covariates that we controlled for in each model are specified when a model is presented. The statistical packages STATA (38) and R (39) were used to carry out the analyses, with a P-value < 0.05 considered statistically significant.

The validated Motivational Interviewing Treatment Integrity (MITI) coding tool (version 4.2.1) was used to assess MI intervention fidelity.(40) The coding entailed making 'Global Ratings' (on 4 dimensions: Cultivating change talk, Softening sustain talk, Partnership and Empathy) and 'Behaviour' counts (with respect to the items: giving information, persuade, persuade with permission, question, simple reflection, complex reflection, affirm, seeking collaboration, emphasising autonomy and confront). A score was assigned to each of these items and the scores compared against the competency and proficiency thresholds that are specified in the MITI manual.

For the analysis of the costs, all costs were collected in South Africa Rand (ZAR) except for the data management system subscription. Results are presented in both ZAR and US dollar ($) using the 2019 OECD exchange rate (1 USD = 14.448 Rand).(36) No South African specific valuation set was available for EQ-5D-3L. The valuation set of Argentina, based on a Visual Analogue Scale, was used to derive utility values, because the GDP per capita in international dollars was the closest between the two countries at the time of analysis.(37,41) Quality-adjusted life years (QALYs) were derived from the utility values at the time points by calculating the area under the curve.(42) No missing data imputation was performed.

RESULTS

Participant enrolment and follow-up

A total of 2099 patients with TB were screened for eligibility out of which 574 consenting and eligible participants were randomised: 291 to control and 283 to intervention. Trial recruitment was terminated on 31 August 2019 before the planned sample size was reached because of budget and time constraints. In the intervention arm, 227 (80.2%) participants completed the first MI (MI 1) session, 199 (70.3%) MI 2 and 150 (53.0%) MI 3. In the intervention arm, at least one message was delivered to 208 (73.5%) participants, while 99 (35.0%) received all messages. Of those randomised to the control and intervention groups, the primary outcome was recorded in 244 (83.8%) and 253 (89.4%) participants, respectively. (Figure 1)

Figure 1 Consort flow diagram

Baseline participant characteristics of the intervention and control arm

Socio-demographic; socio-economic and clinical characteristics

Baseline characteristics were distributed similarly in the intervention and control arms for most variables but with some imbalances in educational level. A total of 513 (91.3%) participants were new patients with TB, 129 (22.5%) women, and nearly all had PTB (International Classification of Diseases-10 A15) without extrapulmonary TB manifestations (553 (98.9%)). About half of the participants were HIV positive (305 (53.2%)), of whom 204 (65.4%) were on cotrimoxazole and 257 (82.4%) were on ART. (Table 1) Details of marital status, employment, wealth, depression status and co-morbidities are presented in Supplementary table 1.

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Table 1 Baseline descriptive socio-economic statistics and clinical characteristics by study arm

	Control (N = 291) n (%)*	Intervention (N = 283) n (%)*	Total (N=574) n (%)*
Age in years: mean (SD)	39.37 (12.60)	38.56 (11.15)	
Female Sex	69 (23.7)	60 (21.2)	129 (22.5)
Education			
No education	7 (2.4)	5 (1.8)	12 (2.1)
Grades 1-5	23 (7.9)	20 (7.1)	43 (7.5)
Grades 6-7	32 (11.0)	35 (12.4)	67 (11.7)
Grades 8-11	96 (33.0)	128 (45.2)	224 (39.0)
Grade 12	87 (29.9)	70 (24.7)	157 (27.4)
Higher	24 (8.2)	8 (2.8)	32 (5.6)
Declined to answer**	22 (7.6)	17 (6.0)	39 (6.8)
TB Patient category			
New patient	264 (92.3)	249 (90.2)	513 (91.3)
Relapse	10 (3.5)	9 (3.3)	19 (3.4)
Re-treatment after default	9 (3.1)	14 (5.1)	23 (4.1)
Re-treatment after failure	1 (0.3)	2 (0.7)	3 (0.5)
Other	2 (0.7)	2 (0.7)	4 (0.7)
TB Site of disease Pulmonary only (ICD-10 A15)	281 (98.9)	272 (98.9)	553 (98.9)
TB Sputum smear, Gene XPert, or culture result available N=	236	227	463
At least one Sputum smear, Gene XPert, or culture result positive	208 (88.1)	195 (85.9)	403 (87.0)
HIV status			
Negative	118 (40.7)	125 (44.2)	243 (42.4)
Positive	163 (56.2)	142 (50.2)	305 (53.2)
Unknown	9 (3.1)	16 (5.7)	25 (4.4)
HIV positive patients			
Using Cotrimoxazole	104 (63.8)	100 (67.1)	204 (65.4)
Using anti-retroviral	139 (85.3)	118 (79.2)	257 (82.4)

* Frequencies and (percentages) are presented unless otherwise stated
**More variables with the option "declined to answer" are listed in the Supplementary table 1

Table 2 Baseline descriptive alcohol and smoking characteristics by study arm

	Control (N=291) n (%)*	Intervention (N=283) n (%)*	Total (N=574) n (%)*
In the past month, smoked tobacco			
Not at all**	110 (37.8)	92 (32.5)	202 (35.2)
Daily	149 (51.2)	149 (52.7)	298 (51.9)
Less than Daily	32 (11.0)	42 (14.8)	74 (12.9)
Had a drink in the past 12-months	208 (71.5)	223 (78.8)	431 (75.1)
AUDIT Score (males) : mean (SD) [max: 19]†	12.27 (3.98)	13.02 (3.78)	12.66 (3.89)
AUDIT Score (females): mean (SD) [max: 19]†	11.32 (4.02)	10.98 (4.02)	11.15 (4.0)
Hazardous/harmful drinking and Smoking Combined (Constructed)			
Hazardous/harmful drinking Only‡	110 (37.8)	92 (32.5)	202 (35.2)
Smoking Only	103 (35.4)	77 (27.2)	180 (31.4)
Smoking and hazardous/harmful drinking‡	78 (26.8)	114 (40.3)	192 (33.4)

* Frequencies and (percentages) are presented unless otherwise stated
**Non-smokers were only included if they were harmful or hazardous drinkers
†Only hazardous/harmful drinkers and/or current smokers were included in the study. Therefore, patients with TB were excluded if they were non-current smokers and had an AUDIT score <7 (females) or <8 (males) or >19; however, they were included if they were smokers independent of whether they had a drink in the past year and therefore independent of the AUDIT score. These AUDIT scores are thus representative of the mean AUDIT scores in the entire study sample and differ from the AUDIT score in the harmful/hazardous drinkers whose change in AUDIT score was measured at 3 and 6-months follow-up
‡Harmful/hazardous drinking is defined as Alcohol Use Disorders Identification Test (AUDIT) score ≥ 8 for men or ≥ 7 for women but <20

There were 372 current smokers (298 daily, 74 less than daily). Seventy eight participants (26.8 %) in the control arm were dual smokers *and* drinkers compared to 114 (40.3 %) in the intervention arm. In the control arm, 110 (37.8%) were hazardous/harmful drinkers only and 103 (35.4%) were smokers only, compared to 92 (32.5%) and 77 (27.2) respectively, in the intervention arm. (Table 2) More details of smoking and drinking history, forms of tobacco use, addiction and quit attempts are presented in Supplementary Table 2.

Primary outcome

Overall, 396 (70%) of participants were classified as treated successfully (treatment completed or cured). The remainder either interrupted treatment, failed treatment, developed drug resistance, were transferred out or had an unknown treatment outcome.(Supplementary table 3) The percentage of successful TB treatment did not differ significantly between the control and intervention arm (70.1% vs. 67.8%), odds ratio (OR) for successful TB treatment 0.90 (95%CI: (0.64,1.27)) comparing the intervention arm to the control arm; and was similar to adjusted ORs (Tables 3 and 4).

Secondary outcomes

Cure rates

Among the 403 participants who had at least one positive bacteriological result at baseline, 168 (41.7%) were recorded as cured; of these, 83/205 (39.9%) were in the control arm compared to 85/195 (43.6%) in the intervention arm. The OR of being cured was 1.16 (95% CI: 0.83,1.63) in the intervention versus the control arm; and was similar to the adjusted OR. (Tables 3 and 4)

Continuous smoking abstinence

Among those who identified as cigarette smokers at baseline (345 (60.1%)), 27 had information (self-report plus biochemical verification) to enable the identification of continuous abstinence at 6-months of which 22 had continuously abstained from smoking. These were similarly distributed across the two study arms: 10 (5.59%) participants in the intervention arm compared to 12 (7.23%) in the control arm, OR 0.76 (95% CI: 0.35,1.63). (Tables 3 and 4) At the 3-month follow-up 20 (11.2%) participants in the intervention arm compared to 27 (16.3%) in the control arm continuously abstained from smoking, OR 0.65 (95% CI: 0.37,1.14). (Tables 3 and 5)

TABLE 3 Descriptive statistics for primary and secondary outcomes by study arm at baseline (where available), 3-months (where available) and 6-months

	Baseline n (%)*			3-months follow-up n (%)*			6-months follow-up n (%)*		
	Control	**Intervention**	**Total**	**Control**	**Intervention**	**Total**	**Control**	**Intervention**	**Total**
TB treatment status[a]									
Successful**							204 (70.1)	192 (67.8)	396 (69.0)
Not Successful							87 (29.9)	91 (32.16)	178 (31.01)
Cured [a, ***									
Yes							83 (39.9)	85 (43.6)	168 (41.7)
No							125 (60.1)	110 (56.4)	235 (58.3)
Continuous smoking abstinence[b]									
Yes				27 (16.3)	20 (11.2)	47 (13.6)	12 (7.2)	10 (5.6)	22 (6.4)
No				139 (83.7)	159 (88.8)	298 (86.4)	154 (92.8)	169 (94.4)	323 (93.6)
Harmful/hazardous drinkers[l]: N =	188†	206†	394†	141†	130†	271†	112†	127†	239†
AUDIT score: mean (SD)	12.76 (3.42)	13.12 (3.47)	12.94 (3.45)	8.28 (6.18)	8.84 (5.38)	8.55 (5.81)	8.79 (6.66)	8.70 (5.83)	8.74 (6.22)
Difference from baseline: mean (SD)				-4.61 (6.26)	-4.07 (5.33)	-4.35 (5.83)	-4.25 (6.56)	-4.17 (6.61)	-4.21 (6.57)
HIV positive patients:	163† (56.2)	142† (50.2)	305† (53.2)	122†	83†	205†	100†	83†	183†
Taking ART medication if HIV positive‡	139 (85.3)	115 (81.0)	254 (83.3)	91 (74.6)	58 (69.9)	149 (72.7)	80 (80.0)	74 (89.2)	154 (84.2)

ART medication adherence[b]						
Optimal adherence	101 (99.0)	64 (98.5)	165 (98.8)	75 (97.4)	64 (97.0)	139 (97.2)
Suboptimal adherence	1 (1.0)	1 (1.54)	2 (1.2)	2 (2.6)	2 (3.0)	4 (2.8)
TB medication adherence						
Optimal adherence	181 (92.3)	138 (90.8)	319 (91.7)	61 (89.7)	59 (90.8)	120 (90.2)
Suboptimal adherence	15 (7.6)	14 (9.2)	29 (8.3)	7 (10.3)	6 (9.2)	13 (9.8)

a: only assessed at 6-months

b: assessed at 3 and 6-months; this table refers to *cigarette* smokers only (other forms of tobacco smoking are excluded)

* Frequencies and (percentages) are presented unless otherwise stated

**Primary Outcome: This is a binary variable defined as either successful treatment (cured or treatment completed) or failed treatment, death, acquired drug resistance, loss to follow-up or treatment interrupted for more than 2 months, or outcome not evaluated/unknown.

***Based on having a cured treatment outcome among those who were bacteriologically positive at baseline.

! hazardous/harmful drinkers who are not alcohol dependent= AUDIT score ≥ 8 for men or ≥ 7 for women but < 20; *! Important distinction at baseline for eligibility purposes.

†Denominator for the mean (SD) or denominator for %

‡ Information on HIV-positivity was obtained from information from TB records combined with patient self-report at baseline. True HIV-positivity rates may have been higher.

TABLE 4 Regression analysis results for the primary and secondary outcomes at 6-months

	Crude Odds Ratio (95% CI)*	P Value*	Adjusted Odds Ratio (95% CI)*	P Value*
Primary outcome				
TB treatment status: Successful (Ref: Not successful)	0.90 (0.64,1.27)	0.548	0.86‡ (0.60,1.24)	0.421
Secondary outcomes				
Cured (Ref: Not Cured)	1.16 (0.83,1.63)	0.374	1.07‡ (0.76,1.51)	0.684
Continuous smoking abstinence (Ref: No)***	0.76 (0.35,1.63)	0.482		
TB medication adherence (Ref: Optimal)	0.89 (0.26,3.07)	0.849		
ART medication adherence (Ref: Optimal)	1.17 (0.14,9.94)	0.884		
Taking ART medication (Ref: No)	2.05! (0.80,5.27)	0.136		
AUDIT	-0.04** (-2,1.91)	0.966	0.02!! (-1.55,1.6)	0.976

* Analyses accounted for potential clustering by centre.
‡ Adjusted for district, sex, and smoking/drinking status and HIV status at baseline. It is worth noting that of the variables in the adjusted model; the only statistically significant result is for the district variable.
! Adjusting for art status at baseline
**Controlling for the AUDIT baseline values. The values represent the study arm regression coefficient.
!! Controlling for the AUDIT baseline values and adjusted for district, sex, and smoking/drinking status and HIV status at baseline. The values represent the study arm regression coefficient.
***Given the limited number of those who were identified as continually abstained, we were only able to adjust for one additional variable at a time. Adding one of the following variables: heaviness of smoking, type of drinker at baseline, age when started smoking, and the duration of smoking at baseline; the adjusted odds ratio of continuous abstinence comparing the intervention to the control arm ranged between 0.73 and 0.76 with similar confidence limits as for the crude estimate

TABLE 5 Regression analysis results for secondary outcomes measured at 3-months

Secondary outcome	Crude Odds Ratio (95% CI)*	P Value*	Adjusted Odds Ratio (95% CI)*	P Value*
Continuous smoking abstinence (Ref: No)**	0.65 (0.37,1.14)	0.135		
TB medication adherence (Ref: Optimal)	1.22 (0.52,2.87)	0.641		
ART medication adherence (Ref: Optimal)	1.58 (0.10,26.12)	0.750		
Taking ART medication (Ref: No)	0.79! (0.38,1.65)	0.53	0.74‡ (0.35,1.58)	0.443
AUDIT	0.55† (-1.01,2.11)	0.474	0.74!! (-0.62,2.1)	0.273

*Analyses accounted for clustering.
! Adjusting for art status at baseline
‡ Adjusted for art status at baseline, district, sex, and smoking/drinking status and HIV status at baseline.
†Controlling for the AUDIT baseline values. The values represent the study arm regression coefficient.
!! Controlling for the AUDIT baseline values and adjusted for district, sex, and smoking/drinking status and HIV status at baseline. The values represent the study arm regression coefficient.
** Given the limited number of those who were identified as continually abstained, we were only able to adjust for one additional variable at a time. Adding one of the following variables: heaviness of smoking, type of drinker at baseline, age when started smoking, and the duration of smoking at baseline; the adjusted odds ratio of continuous abstinence comparing the intervention to the control arm ranged between 0.63 and 0.66 with similar confidence limits as for the crude estimate.

Change in harmful/hazardous drinking

AUDIT scores were about 4 points lower at both follow-up times than at baseline, independent of the intervention.(Table 3) In the intervention arm, participants had, on average, a reduction of 0.04 points (95% CI: -2,1.91) on the AUDIT score at 6-months, compared to those in the control arm controlling for baseline scores; whereas an average increase of 0.55 (95% CI: -1.01,2.11) was observed at 3-months. (Tables 4 and 5)

Medication adherence and ART uptake

At 6-months, the OR of taking ART medication was 2.05 (95% CI: 0.80,5.27) comparing the intervention arm to the control arm and controlling for ART baseline medication status; whereas it was 0.79 (95% CI: 0.38,1.65) at 3-months. The proportion of participants who had optimal TB medication adherence was 90.2% (120/133) at 6-months and 91.7% (319/348) at 3-months. Suboptimal TB medication adherence ORs were 0.89 (95%CI: 0.26,3.07) and 1.22 (95%CI: 0.52,2.87) comparing intervention arm to the control arm at 6-months and 3-months, respectively. The proportions of participants on ART who had optimal ART medication adherence were high at both 3-months (165/167, 98.8%) and 6-months follow-up (139/143, 97.2%). Suboptimal ART medication adherence ORs were 1.17 (95%CI: 0.14,9.94) and 1.58 (95%CI: 0.10,26.12) comparing the intervention arm to the control arm at 6-months and 3-months, respectively. (Tables 3, 4 and 5)

Intervention fidelity

Motivational interviewing fidelity

The recordings of 17 counsellors (one each) were transcribed verbatim and then assessed. In terms of the global ratings, the LHWs' counselling sessions were above proficiency levels on all items, namely, cultivating change talk, softening sustain talk, partnership, and empathy (as the mean scores were all above 2). In terms of the summary measures, the LHWs' counselling sessions did not achieve the basic proficiency threshold of 3.5 for the Relational component (Partnership + Empathy) as their mean score was 3.1 (SD=1.19). However, their mean score on the Technical component (Cultivating Change Talk + Softening Sustain Talk) of 3.3 (SD=0.97) was above the threshold of 3. For behavioural counts, "Asking Questions" had the highest mean score (24.2; SD=10.42), followed by "Affirm" with a mean score of 5.5 (SD=3.7). The counsellors were least likely to engage in the following: Persuade with permission and emphasising autonomy. The mean Reflections to Questions Ratio was 0.23 (SD=0.24). The LHWs made on average 9.3 (SD=4.74) MI adherent (Affirm, Emphasize Autonomy and Seek Collaboration) and 1.2 (SD=2.28) MI non-adherent (Confront and Persuade) statements per session. (Supplementary Table 4)

SMS-delivery

Of the total number of Information-Motivation-Behaviour messages triggered, 3583 (80.4%) were delivered. All due SMS messages were delivered to 95 (41.9%) of the participants who completed the first MI, See Supplementary Table 5 for more details.

Costs and health related quality of life

Unit costs used to estimate the mean costs are presented in the Supplementary Table 6. Incremental cost-utility ratios are not presented since the intervention was not clinically effective. The mean cost of the ProLife intervention was ZAR 2601 (SD 6) ($180.02 (SD $0.42)) per participant in the intervention arm (n=283). The mean cost of usual care was ZAR 681 (SD 357) ($47.13 (SD $24.71)) in the intervention arm (n=122) versus ZAR 706 (SD 302) ($48.86 (SD $20.90)) in the control arm (n=131). The total mean cost of care including the intervention was ZAR 3285 (SD R357) ($227.37 (SD 24.71)) in the intervention arm (n=122). EQ-5D-3L data were available at the 3 time points for 137 intervention and 159 control arm participants. The mean QALYs estimated over six months were 0.442 (SD 0.061) in the intervention arm versus 0.430 (SD 0.074) in the control arm (adjusted mean difference 0.006 (95% CI -0.001 to 0.013)).

DISCUSSION

This RCT did not provide evidence for improved TB treatment success rates in those receiving the ProLife intervention compared to those receiving usual care. We could also not demonstrate significant beneficial effects on any of the secondary outcomes, i.e., smoking, alcohol consumption, medication adherence and ART initiation. To our knowledge there are no other published studies of similar complex interventions that aim to improve TB treatment outcomes in patients who smoke or drink to harmful or hazardous extent. Interventions evaluated by other studies were either complex interventions or SMS-based interventions aimed at improving TB outcomes through the pathway of increasing adherence, but without an alcohol or smoking intervention component (43,44) or focused on a single behaviour, namely smoking or drinking.(45,46). Of the latter studies, a brief smoking cessation intervention was effective in inducing smoking cessation in patients with TB but did not improve TB outcomes.(45) Conversely, in another study in India, intensive counselling for alcohol disorders led to significantly better TB treatment outcomes in the intervention group compared to the control group.(46) Smoking cessation also led to better TB treatment outcomes in a secondary analysis of a large tobacco cessation trial in patients with TB in Bangladesh and Pakistan.(47) Our

non-significant result for smoking-related outcomes is not consistent with findings from our previous TB study, which used a single MI session and found that the chance of sustained smoking cessation was twice as high in the MI intervention group compared to the control group,(14) albeit with a less stringent exhaled CO cut-off point. Evidence on the effectiveness of MI for smoking abstinence in non-TB settings has been equivocal.(48) Self-reported alcohol consumption decreased with about 4 points in both intervention and control arms in our study at both follow-up times. Answering questions on drinking in brief intervention trials may alter subsequent self-reported behaviour: exposing non-intervention control groups to an integral component of the intervention may therefore underestimate the effect of the intervention.(49) There have been few previous studies looking at MI and SMS interventions for the modification of hazardous/harmful drinking in the context of TB. A previous trial of a brief counselling intervention to reduce alcohol consumption in patients with TB did not find a significant effect on alcohol reduction.(50) Outside a TB setting, results have been mixed. A meta-analysis showed a small but significant improvement in outcomes when MI was used in conjunction with cognitive behavioural therapy for co-morbid alcohol use and depression.(51) Self-reported TB and ART medication adherence was high overall in our study population, which is consistent with other studies conducted in South Africa.(52,53) It is possible that we did not find a difference in treatment adherence due to a ceiling effect.

There were several key strengths in this RCT. This was an individually RCT with a relatively large sample size and a high follow up rate (87%) for the primary outcome. Primary outcome assessment was blinded. This was a novel intervention, which built on previous successes with both MI and mHealth interventions and was aligned with the WHO's call to increase the use of digital technologies to improve TB care.(15) We utilized a validated alcohol consumption questionnaire (AUDIT) (29) and a four-day timeline follow-back for medication adherence to reduce recall bias as self-reports tend to underreport drinking while overestimating adherence behaviour compared with.(54) (35) Smoking cessation was confirmed with exhaled CO using strict cut-off points. Overall, the quality of the counselling was acceptable. The results of our MI analyses suggest that the LHWs trained as counsellors were more proficient in MI than during the feasibility stage, as observed by their global rating scores on cultivating change talk, softening sustain talk, partnership and empathy. (Supplementary Table 4) These results were achieved by ongoing monitoring and training of LHWs during the trial and adapting the training based on feedback from the feasibility stage. Extra counsellors were also appointed to minimise travel distances to clinics. There were some limitations associated with this RCT. Trial recruitment had to be terminated before the planned sample size because of funding and time constraints. Nevertheless, the calculation of sample size was based on

an anticipated 25% LTFU for the primary outcome, while in reality only 13.4 %, of the TB outcomes were not available. As a result, we achieved a slightly higher power to detect the a 10% difference in primary outcomes, than we had aimed for (83% vs. 80%). The smaller sample size did however reduce the power to detect a difference for secondary outcomes for which the LTFU was much higher than 25%. Also, the calculated sample size was not powered for subgroup analysis which was the case for outcomes relating to smoking, drinking, ART and cure rates. In addition, due to COVID-19 lockdown in March 2020, we had to switch to telephonic follow-up of participants using a shortened questionnaire (22 participants) and could not access clinics to retrieve outstanding TB treatment outcomes. The low intervention uptake meant that half of the participants received only one or two MI sessions combined with SMS messages. SMS messages were only used for the first half of the study period, and one quarter of participants did not receive their messages, a commonly occurring problem in developing countries.(20,55) It could be argued that in the absence of ongoing text messages, the MI and associated text messages were not enough to keep participants focussed for the second three months of the trial. The 2-arm study design did not permit the untangling of the individual effects of SMS and MI. Understanding their separate effects could have important cost implications as SMS-communication would be cheaper and easier to organise than individual counselling.

The lack of effectiveness of our intervention on the primary outcome (TB treatment success) can have a number of possible explanations. Although intervention uptake was high (80.2%) for the first counselling session, many participants did not return for the second (29.7%) and third (47%) sessions. As a result of this only about half of the intervention arm participants received all three MI sessions. Furthermore, about one quarter of all participants did not receive any SMS-messages. Low intervention uptake leads to a dilution of any potential effects. The lack of effectiveness on TB treatment success could perhaps also be explained by the complexity of the ProLife intervention itself: counsellors had to address multiple behaviours, namely medication adherence, tobacco smoking and hazardous/harmful drinking. Despite having established the feasibility and acceptability of this approach (31) and ongoing on site performance monitoring and feedback of counsellors, it is possible that MI for multiple behaviour change in the ProLife study was counterproductive as counsellors may have ended up not focusing on any of the behaviours at optimal levels. Similarly, patients might have found it difficult to change multiple behaviours simultaneously, especially because smoking and drinking are mutually reinforcing. This integrated approach was nevertheless adopted to avoid the need for multiple vertical counselling services (in addition to TB treatment and HIV treatment), to allow the different elements of the programme to reinforce one another, and to improve the affordability, feasibility and acceptability for a future roll-out of the programme. It is

also possible that sequential interventions may be better, at least for smoking cessation.(56) More intensive counselling (more sessions) or a modified counselling method may have been more appropriate, even more so since a recent review of reviews of MI casts doubt on its efficacy.(48,57,58) For example, more emphasis on increasing patient knowledge in addition to increasing self-efficacy may have been more effective.(59) The cause of the mobile health message delivery problems (such as poor network coverage, no electricity to charge phones) (60) would need to be investigated in order to increase the effectiveness of future mHealth interventions. Messages may also have to be intensified or modified to be more interactive and/or tailored to specific circumstances of each individual. This would improve the personal value of the intervention to the individual, which is likely to increase the chances of their participation in the intervention.(61) Consistent with the normalisation process theory,(62) cognitive participation in the intervention might have been higher had we been deliberate in the implementation to ensure the TB nurse who would have routinely seen the participants, provided additional support and motivated participants to attend MI sessions with the counsellor. In this way, the intervention would have gained 'legitimacy' but this would have led to unblinding of the nurses to the intervention arm.

In conclusion, we could not demonstrate that the ProLife intervention was effective in improving TB treatment outcomes. This may be due to the lack of effect of the intervention, but the study may also have been underpowered for the intermediary secondary outcomes. Valuable lessons were learnt on challenges relating to training LHWs in MI counselling and delivery, SMS-delivery in a challenging socio-economic context and the reasons for loss to follow-up of TB participants with multiple health problems. Further research is needed to provide answers on how to increase intervention uptake in poor resource settings and whether our complex intervention should have been more intensive. Other important questions are whether another counselling method would have been more effective. Lastly, in the light of the already existing evidence of SMS and the costs and implementation challenges relating to MI, intervention studies limited to an mHealth intervention but using different intensities, duration and type of interventions (one-way, two-way, interactive) are needed.

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Contributors

MK contributed to study design and the manuscript, led on the sample size determination and did the statistical analysis. NKM contributed to study design, particularly with respect to development of the MI intervention, did the analysis of the MI data and contributed to the manuscript writing. AVZ led the data management and SMS-system, monitored data quality and contributed to data analysis and manuscript writing. ASM contributed to study design and led on the preparation of the manuscript. NDM contributed to study design, intervention development and manuscript preparation. JL and SP led on the economic evaluation. AT contributed to the economic evaluation. JT was site lead for the Bojanala sub-district. OBO was site lead for the Sedibeng sub-district. MOB contributed to study design, data interpretation and the manuscript. KS and OAA are co-principal investigators. Both contributed to study design, data interpretation and manuscript writing. All authors read and approved the final draft of the manuscript.

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Competing interests

OA Ayo-Yusuf, the principal investigator, received a research grant (MRC-RFA-02: TB -05-2015) which was allocated to Sefako Makgatho Health Sciences University to pay for the expenses related to the research project. As co-prinicipal investigator K Siddiqi received part of the MRC-Newton research grant (MRC-RFA-02: TB -05-2015) which was allocated to the University of York to support the research by the authors affiliated to the University of York (K Siddiqi, ND Mdege, M Kanaan, S Parrot, J Lee). Goedele Louwagie received a small monthly remuneration per month from 1 October 2018 until 30 June 2020 as academic research coordinator. André van Zyl was employed as a research data manager on a part-time basis from 1 September 2017 and 30 June 2020. OA Ayo-Yusuf received support for attending meetings and for travel by Tax Justice Network Africa. He is the Vice Chair of the Standing Committee on Health, Academy of Science, SA (not remunerated). The remaining authors declare no competing interests.

Ethical considerations

This study received ethics approval from the Research Ethics Committees of: Sefako Makgatho Health Sciences University (SMU; Ref: SMUREC/D/234/2017: IR); the South African Medical Research Council (with the SMU Ethics Committee serving as the Research Ethics Committee Record); the University of Pretoria (Ref: 434/2017); the University of Witwatersrand (M160455); and the University of York (no reference number, approval date 15 January 2017 (29).

Patient Consent for publication

Not applicable

Data availability statement

The study protocol was previously published.(30) The de-identified participant and SMS data sets are stored in labelled Stata files and are accompanied by a statistical analysis plan and metadata explaining each variable. Although data can be viewed immediately, data will be embargoed for data analysis until 30 June 2023. Thereafter, permission must be obtained from the principal investigators (OA and KS) for any data

analysis not yet performed by the primary research group. Data are stored in the institutional data repository at Sefako Makgatho Health Sciences University called Discover research (https://smu-za.figshare.com/) with a CC-BY 4.0 (Attribution) license (Creative Commons — Attribution 4.0 International — CC BY 4.0). The statistical analysis plan is available as supplementary material.

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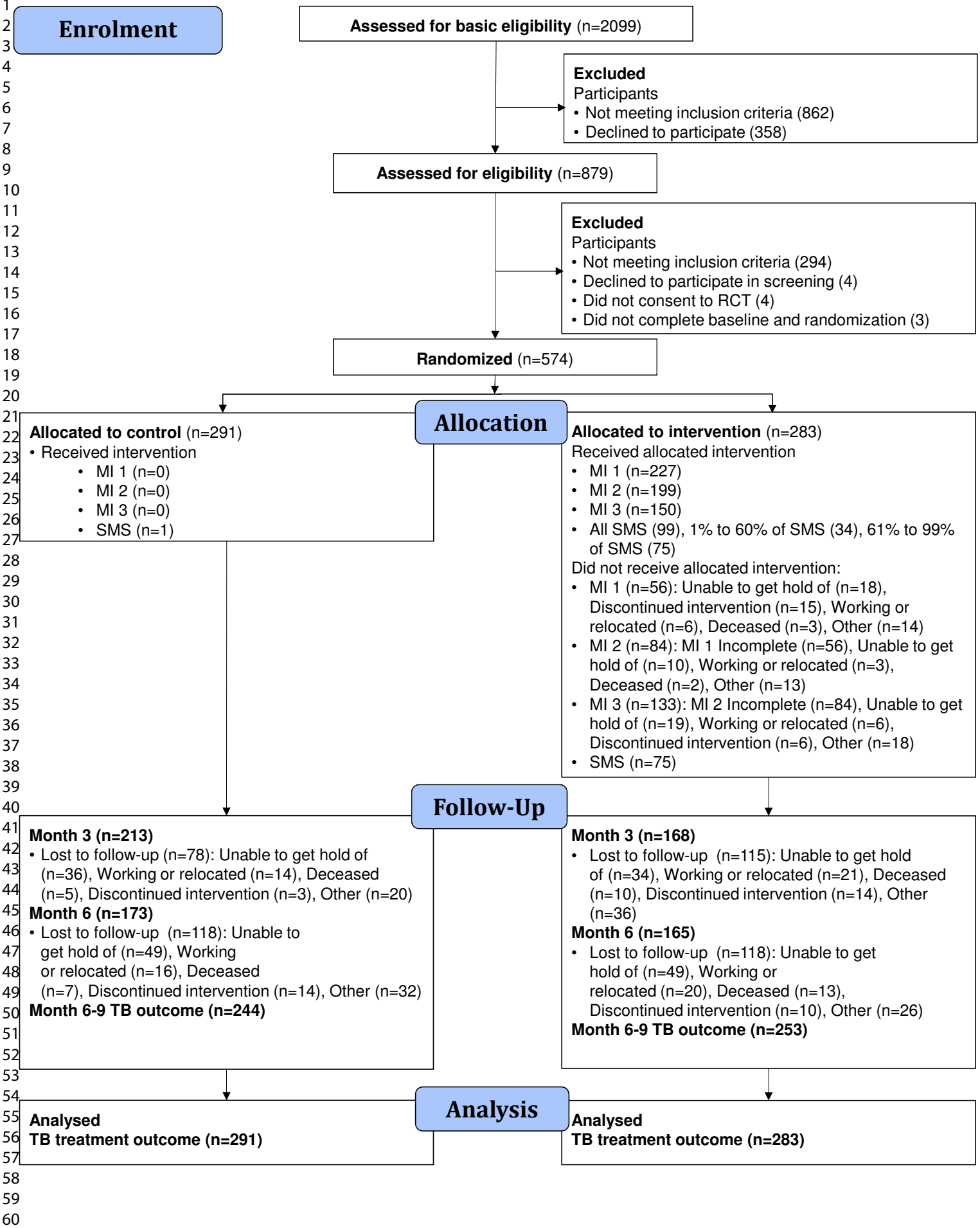
Enrolment
Assessed for basic eligibility (n=2099)
Excluded
Participants
• Not meeting inclusion criteria (862)
• Declined to participate (358)
Assessed for eligibility (n=879)
Excluded
Participants
• Not meeting inclusion criteria (294)
• Declined to participate in screening (4)
• Did not consent to RCT (4)
• Did not complete baseline and randomization (3)
Randomized (n=574)
Allocation
Allocated to control (n=291)
• Received intervention
• MI 1 (n=0)
• MI 2 (n=0)
• MI 3 (n=0)
• SMS (n=1)
Allocated to intervention (n=283)
Received allocated intervention
• MI 1 (n=227)
• MI 2 (n=199)
• MI 3 (n=150)
• All SMS (99), 1% to 60% of SMS (34), 61% to 99% of SMS (75)
Did not receive allocated intervention:
• MI 1 (n=56): Unable to get hold of (n=18), Discontinued intervention (n=15), Working or relocated (n=6), Deceased (n=3), Other (n=14)
• MI 2 (n=84): MI 1 Incomplete (n=56), Unable to get hold of (n=10), Working or relocated (n=3), Deceased (n=2), Other (n=13)
• MI 3 (n=133): MI 2 Incomplete (n=84), Unable to get hold of (n=19), Working or relocated (n=6), Discontinued intervention (n=6), Other (n=18)
• SMS (n=75)
Follow-Up
Month 3 (n=213)
• Lost to follow-up (n=78): Unable to get hold of (n=36), Working or relocated (n=14), Deceased (n=5), Discontinued intervention (n=3), Other (n=20)
Month 6 (n=173)
• Lost to follow-up (n=118): Unable to get hold of (n=49), Working or relocated (n=16), Deceased (n=7), Discontinued intervention (n=14), Other (n=32)
Month 6-9 TB outcome (n=244)
Month 3 (n=168)
• Lost to follow-up (n=115): Unable to get hold of (n=34), Working or relocated (n=21), Deceased (n=10), Discontinued intervention (n=14), Other (n=36)
Month 6 (n=165)
• Lost to follow-up (n=118): Unable to get hold of (n=49), Working or relocated (n=20), Deceased (n=13), Discontinued intervention (n=10), Other (n=26)
Month 6-9 TB outcome (n=253)
Analysis
Analysed
TB treatment outcome (n=291)
Analysed
TB treatment outcome (n=283)

SUPPLEMENTARY TABLES

Supplementary table 1 Detailed baseline descriptive statistics for socio-demographic, socio-economic, and clinical characteristics by study arm			
	Control (N = 291) n (%)*	Intervention (N = 283) n (%)*	Total (N=574) n (%)*
Marital status			
Married or living together	102 (35.1)	95 (33.6)	197 (34.3)
Divorced/separated	20 (6.9)	18 (6.4)	38 (6.6)
Widowed	10 (3.4)	7 (2.5)	17 (3.0)
Never married and never lived together	144 (49.5)	150 (53.0)	294 (51.2)
Declined to answer	15 (5.2)	13 (4.6)	28 (4.9)
Employment			
Self-employed (full-time)	30 (10.3)	36 (12.7)	66 (11.5)
Employed full-time (30 hrs a week or more)	62 (21.3)	54 (19.1)	116 (20.2)
Employed part-time (less than 30 hrs a week)	19 (6.5)	29 (10.2)	48 (8.4)
Retired	17 (5.8)	16 (5.7)	33 (5.7)
Unemployed (but able to work)	125 (43.0)	120 (42.4)	245 (42.7)
Unable to work because of long-term disability or ill health	9 (3.1)	8 (2.8)	17 (3.0)
Full-time student	12 (4.1)	4 (1.4)	16 (2.8)
Caring from my home and family/doing household work/housewife	0 (0.0)	2 (0.7)	2 (0.3)
Occasional work (“piece job”)	17 (5.8)	12 (4.2)	29 (5.1)
Declined to answer	0 (0.0)	2 (0.7)	2 (0.3)
Ever worked or spent time in mines			
No	244 (83.8)	237 (83.7)	481 (83.8)
Yes	46 (15.8)	45 (15.9)	91 (15.9)
Household items (Yes is displayed)			
A radio	249 (85.6)	234 (82.7)	483 (84.1)
A television	255 (87.6)	255 (90.1)	510 (88.9)
A landline telephone	21 (7.2)	22 (7.8)	43 (7.5)
A desktop or laptop computer	67 (23.0)	48 (17.0)	115 (20.0)
A refrigerator	248 (85.2)	240 (84.8)	488 (85.0)
A vacuum cleaner or floor pol	49 (16.8)	35 (12.4)	84 (14.6)
A microwave oven	198 (68.0)	189 (66.8)	387 (67.4)
An electric or gas stove	254 (87.3)	238 (84.1)	492 (85.7)
A washing machine	153 (52.6)	136 (48.1)	289 (50.3)
Total number of assets: mean (SD)	5.14 (1.96)	4.94 (1.77)	5.04 (1.87)
In the past month, number of days you or people in the household went to bed hungry because there was no food to eat			
0 days	244 (83.8)	238 (84.1)	482 (84.0)
1-7 days	45 (15.5)	34 (12.0)	79 (13.8)
More than 7 days	2 (0.7)	9 (3.2)	11 (1.9)
Declined to answer	0 (0.0)	2 (0.7)	2 (0.3)
Number of pre-treatment smear tests recorded?			

One	197 (92.1)	169 (87.6)	366 (89.9)
Two	17 (7.9)	24 (12.4)	41 (10.1)
Number of Gene XPert results recorded			
One	225 (97.8)	210 (97.2)	435 (97.5)
Two	5 (2.2)	6 (2.8)	11 (2.5)
Number of culture results recorded on the TB Treatment record			
One	54 (94.7)	42 (97.7)	96 (96.0)
Two	3 (5.3)	1 (2.3)	4 (4.0)
Co-morbidities			
Hypertension	19 (6.93)	11 (4.1)	30 (5.54)
Diabetes	5 (1.84)	4 (1.49)	9 (1.66)
Epilepsy	3 (1.09)	4 (1.49)	7 (1.29)
Mental illness	3 (1.09)	0 (0)	3 (0.55)
Liver disease	1 (0.36)	1 (0.38)	2 (0.37)
Renal insufficiency	1 (0.36)	1 (0.38)	2 (0.37)
Allergies	2 (0.76)	0 (0)	2 (0.38)
Other	1 (0.36)	1 (0.38)	2 (0.37)
Depression score (CESD 10): mean (SD)	8.44 (4.38)	8.74 (4.8)	8.59 (4.59)

*Counts and percentages unless otherwise indicated

Supplementary table 2 Detailed descriptive statistics for smoking history, alcohol history at baseline by study arm

	Control n (%)*	Intervention n (%)*	Total n (%)*
Smoking History (current smokers only) N=	181	191	372
On the days that you smoke, how soon after you wake up do you have your first cigarette?			
After 60 minutes	30 (16.6)	28 (14.7)	58 (15.6)
31-60 minutes	24 (13.3)	16 (8.4)	40 (10.8)
6- 30 minutes	60 (33.1)	65 (34.0)	125 (33.6)
Within 5 minutes	67 (37.0)	82 (42.9)	149 (40.1)
Duration of smoking in months: mean (SD)	212.09 (134.03)	224.93 (127.82)	218.68 (130.86)
Duration of smoking in months: median (IQR)	186 (110, 282)	206 (135, 294)	200.5 (123, 287)
Age started smoking in years: mean (SD)	19.2 (6.3)	19.3 (6.3)	19.3 (6.3)
Age started smoking in years: median (IQR)	18 (15-20)	18 (16-21)	18 (15.5-20.5)
Form of tobacco used			
Manufactured cigarettes (Yes)	166 (91.7)	179 (93.7)	345 (92.7)
Number of days you smoked in the past 7days: mean (SD)	5.3 (2.65)	5.53 (2.33)	5.42 (2.49)
Average number of cigarettes smoked daily: mean (SD)	6.18 (6.43)	6.48 (8.21)	6.34 (7.39)
Hand-rolled cigarettes (Yes)	14 (7.7)	21 (11.0)	35 (9.4)
Number of days you smoked in the past 7days: mean (SD)	4.71 (2.84)	3.71 (2.95)	4.11 (2.91)
Average number of handrolled cigarettes smoked daily: mean (SD)	3.71 (3.97)	3.81 (2.82)	3.77 (3.27)
Pipe (Yes)	4 (2.2)	2 (1.0)	6 (1.6)
Number of days in the past 7days you smoked: median (IQR)	1 (0, 2.5)	4.5 (2, 7)	2 (0, 3)
Average number of daily sessions: median (IQR)	1 (0, 3.5)	3 (1, 5)	1.5 (0, 5)
Length of one session (on average) in **minutes**: median (IQR)	90 (60, 107.5)	60 (30, 90)	90 (30, 90)
Cigars, cheroots or cigarillos (Yes)	1 (0.55)	0 (0)	1(0.27)
Water pipe (Yes)	3 (1.7)	2 (1.0)	5 (1.3)
Other	10 (5.5)	4 (2.1)	14 (3.8)
Heaviness of smoking index >= 4	134(74.03)	158(82.72)	292(78.49)
Smoking inside your home restrictions			
Total: Not allowed	96 (53.0)	108 (56.5)	204 (54.8)
Some rules: where/when it is allowed	61 (33.7)	58 (30.4)	119 (32.0)
No rules	24 (13.3)	25 (13.1)	49 (13.2)

Attempts to quit smoking (current smokers only)			
Ever attempted to quit in the past (Yes)	52 (28.7)	64 (33.5)	116 (31.2)
Number of attempts to quit: mean (SD)	2.46 (2.98)	2.64 (1.62)	2.56 (2.32)
Time elapsed since attempt to quit last time, in months: mean (SD)	36.65 (94.62)	25.13 (37.91)	30.29 (69.22)
Longest duration abstinent in previous quit attempts: mean (SD)	6.15 (13.48)	4.22 (8.9)	5.09 (11.18)
Likelihood to TRY TO QUIT smoking completely and permanently in the next three months			
Definitely will not	6 (3.3)	5 (2.6)	11 (3.0)
Probably will not	10 (5.5)	12 (6.3)	22 (5.9)
Probably will	104 (57.5)	109 (57.1)	213 (57.3)
Definitely will	61 (33.7)	65 (34.0)	126 (33.9)
Likelihood that I WILL QUIT smoking completely and permanently in the next three months			
Definitely will not	6 (3.3)	5 (2.6)	11 (3.0)
Probably will not	11 (6.1)	13 (6.8)	24 (6.5)
Probably will	103 (56.9)	104 (54.5)	207 (55.6)
Definitely will	61 (33.7)	69 (36.1)	130 (34.9)
Ever used any methods to help you stop smoking tobacco in the past 3-months? (Yes)	23 (12.7)	16 (8.4)	39 (10.5)
Smokeless tobacco use (all participants)			
In the past month, have you used smokeless tobacco (Snuff) on a daily basis			
Not at all	275 (94.5)	275 (97.2)	550 (95.8)
Daily	12 (4.1)	6 (2.1)	18 (3.1)
Less than Daily	4 (1.4)	2 (0.7)	6 (1.0)
Duration of using ST in months: mean(SD)	113.69 (112.7)	152 (91.16)	126.46 (105.61)
Age started using ST in years: mean (SD)	27.56 (10.57)	25.88 (13.43)	27 (11.33)
Form of ST used (for SLT users)			
Snuff (by mouth)	2 (12.5)	0 (0.0)	2 (8.3)
Snuff (by nose)	11 (68.8)	5 (62.5)	16 (66.7)
Chewing tobacco leaves	0(0)	0(0)	0(0)
Other	1 (6.3)	0 (0.0)	1 (4.2)
Help to stop drinking (N= , had a drink in past 12 months)	208	223	431
Ever used any methods to stop drinking alcohol in the past 3-months	21 (11.2)	22 (10.7)	43 (10.9)

* Frequencies and (percentages) are presented unless otherwise stated

Supplementary table 3 Detailed descriptive statistics for primary outcome by study arm at 6-months

TB treatment status detailed	Control n (%)	Intervention n (%)	Total n (%)
Cured	108 (37.1)	105 (37.1)	213 (37.1)
Treatment completed	96 (33.0)	87 (30.7)	183 (31.9)
Treatment interrupted > 2 months	15 (5.2)	29 (10.2)	44 (7.7)
Treatment failure	5 (1.7)	2 (0.7)	7 (1.2)
Acquired drug resistance	1 (0.3)	4 (1.4)	5 (0.87)
Died	11 (3.8)	15 (5.3)	26 (4.5)
Transfer out	8 (2.75)	11 (3.9)	19 (3.31)
Unknown	42 (14.4)	25 (8.8)	67 (11.7)

Supplementary table 4 MI treatment fidelity scores of counselling sessions delivered by 17 lay health workers*

Ratings	Mean (SD)	Range
Global ratings**		
Cultivating change talk	3.2 (1.17)	1-5
Softening sustain talk	3.4 (0.96)	1-4
Partnership	3.4 (1.12)	2-5
Empathy	2.9 (1.34)	1-5
Behaviour counts&		
Giving information	4.8 (8.13)	0-5
Persuade	0.8 (1.48)	0-5
Persuade with permission	0.1 (0.24)	0-1
Question	24.2 (10.42)	12-51
Simple reflection	4.1 (3.21)	0-10
Complex reflection	1.6 (2.69)	0-9
Affirm	5.5 (3.47)	1-12
Seeking collaboration	2.4 (1.46)	0-6
Emphasising autonomy	1.4 (1.37)	0-4
Confront	0.4 (0.74)	0-3
Summary measures		
Total MI non-adherent †	1.2 (2.28)	0-7
Total MI adherent†	9.3 (4.74)	1-16
Technical global ratings**	3.3 (0.97)	1.5-4.5
Relational global ratings**	3.1 (1.19)	1.5-5
Reflection to question ratio††	0.23 (0.24)	0-0.83
Percentage of complex reflections***	20.4 (21.9)	0-67

*The recordings of 17 counsellors (one each) were transcribed verbatim and then assessed. In order to assess the fidelity of the counsellors' delivery of motivational interviewing during the trial, we are used the validated Motivational Interviewing Treatment Integrity Coding Manual 4.2.1 (MITI) tool. The table shows the results of the fidelity assessment that was conducted by one rater who is proficient in English, seSotho and seTswana and in motivational interviewing. The rater listened to the recordings and coded a randomly selected 20-min portion of the written transcript. In the case of shorter counselling sessions, the entire recording was assessed.

**The "global ratings" involve assessing, on a 5-point Likert scale (1 for low and 5 for high), how well or poorly the counsellor adheres to the MI practice. Ratings are conducted on four items, two each making up Technical Components (Cultivating change talk and Softening sustain talk) and Relational Components (Partnership and Empathy).

**Scores on Cultivating Change Talk and Softening Sustain Talk are averaged to obtain the Technical global scores.

***Scores on Partnership and Empathy are averaged to obtain Relational global scores. The basic competency threshold scores for fair and good proficiency are 3 and 4, respectively for Technical scores and 3.5 and 4, respectively for Relational scores.

&The "behaviour counts" involve counting 10 verbal behaviours of the counsellor during the intervention.

† "MI adherence" is determined by adding up the following verbal behaviours: Seeking Collaboration, Affirm and Emphasising autonomy. "MI non-adherence" is determined by summing instances of Confront and Persuade. No thresholds for MI adherence or non-adherence are specified in the MITI 4.2.1.

††The Reflection-to-Question (R:Q) ratio is the total reflections divided by the total questions asked. One reflection to each question is considered a "fair" practice level while two reflections to each question is considered a "good" practice level.

*** The Percentage of Complex Reflections (% CRs) is calculated by dividing the number of complex reflections by the sum of complex reflections and simple reflections. A fair and a good % CRs are 40% and 50%, respectively.

Supplementary table 5 SMS delivery				
			Intervention (N=283)	Control (N=291)
No. of participants who received ALL due IMB messages INDEPENDENT OF WHETHER they completed MI 1			99/283 (35%)	1/291 (0.3%)
Completion of first MI and initiation of SMS-sequence				
Completed first MI			227/283 (80.2%)	0/291 (0%)
No. of participants who received ALL due messages after receipt of MI1			95/227 (41.9%)	0/0 (0%)
SMS delivery for participants for whom the SMS-sequence was initiated (after receipt of first MI)				
	Mean (SD)	Median (IQR) Range	Mean (SD)	Median (IQR) Range
Average no. adherence messages received per participant (n=227)	7.9 (3.5)	10 (8-10) 0-11	0	0
Average no. tobacco-related messages received (n=153)	5.4 (2.5)	7 (5-7) 0-7	0	0
Average no. alcohol related messages received (n=171)	5.5 (2.5)	7 (5-7) 0-7	0	0
Average no. IMB messages received (n= 227)	15.7 (7.3)	17 (13-22) 0-25		

Supplementary table 6 Unit costs used in the analysis (Presented in Rand as sources, $1=R14.448 in 2019)

Item	Unit costs
Personnel	LHWs: R3000/month, 160 hours/month, R18.75/hour; District coordinators: R7500/month, 160 hours/month, R46.88/hour; MRC appointed supervisor: R205.79/hour; Trainers: R373.17/hour; Administrative staff: R333.24/hour
Materials	Training manual: R3250; Printing: R3000; Additional printing & stationary: R500
Accommodation / Travel / Refreshments	LHWs accommodation: R540 000; Trainers accommodation/travel: R36 000; Supervision accommodation/travel: R30 000; Refreshment: R12 500
SMS system	Monthly subscription at R433.44 ($30) for 3-months: R1300
MI sessions	Session 1 (17 minutes): R5.31; Session 2 (16 minutes): R5.00; Session 3 (17 minutes): R5.31
Biochemical investigations	Cost of TB smear microscopy: R28.37; culture: R79.22 and GeneXpert: R201.56 (Source: 2019/20 National Health Laboratory Service pricing schedule)*
ART	Atroiza: R3.78/dose; Dumiva: R5.55/dose; Tenemine: R2.34/dose; Zovilam: R1.72/dose; Kavimun: R1.89/dose; Ricovir: R1.36/dose; Zidomat: R1.38/dose; Lazena: R0.55/dose; Efrin:R0.63/dose; Efamat: R0.63/dose; Acriptaz: R0.61/dose (Source: Western Cape Department of Health. Antiretroviral and TB Stockmaster Worksheet. 2019)
TB medication	Month's supply of RHZE (intensive) @ R65.80; RH (continuation) @ R55.56 (Source: Western Cape Department of Health. Antiretroviral and TB Stockmaster Worksheet. 2019)

PROLIFE

Im*pro*ving TB outcomes by modifying *life*-style behaviours through a brief motivational intervention followed by short text messages (Phase II)

A multi-centre randomised controlled trial looking at the effect of a complex behavioural intervention on TB and lifestyle-related outcomes in South Africa

Version 1.2

Trial Registration number/registry: ISRCTN62728852/ISRCTN registry
http://www.isrctn.com/ISRCTN62728852

Version date: ~~**14 Feb 2020**~~ 25 Oct 2020

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Sponsor	**Olalekan Ayo-Yusuf, Sefako Makgatho University/ University of Pretoria**
Funder	**Newton Fund/MRC**
Funder Reference Number	**MRC-RFA-02: TB -05-2015**

STATISTICAL ANALYSIS PLAN

V1.2

Contents

This analysis plan deals only with the statistical analysis of the trial.

1. Definition of terms

Abbreviation	Expansion
ACTG	AIDS Clinical Trials Group
AE	Adverse Event
ART	Anti-retroviral therapy
AUDIT	Alcohol Use Disorders Identification Test
CI	Confidence Interval
CO	Carbon monoxide
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
EPTB	Extra-pulmonary TB
HIV	Human immunodeficiency virus
LHW	Lay health worker
MI	Motivational interviewing
PTB	Pulmonary TB
SMS	Short Message Service
SA	South Africa
SADHS	South Africa Demographic and Health Survey
SAE	Serious Adverse Event
SD	Standard deviation
SOPs	Standard Operating Procedures
TB	Tuberculosis

2. Trial Objectives

The PROLIFE model is a complex behavioural intervention comprised of a brief motivational interviewing (MI) counselling strategy augmented with subsequent SMS messaging. To be delivered in three brief sessions, the MI intervention will target three main areas, as appropriate:

- Tobacco smoking
- Alcohol drinking
- Tuberculosis (TB) and Anti-retroviral therapy (ART) adherence or ART initiation

Primary objective:

- To assess the effectiveness of the PROLIFE model delivered by lay health workers (LWH) compared to usual care in improving Pulmonary TB (PTB) treatment outcomes

Secondary objective: (**this element will not be addressed in this SAP**)

- To estimate the cost-effectiveness of the PROLIFE model

3. Design

This is a pragmatic, prospective, multicentre, two-arm, parallel, individual RCT taking place in 27 purposively selected primary care clinics with the highest TB case-load in three districts in South Africa: Welkom in the Free State; Bojanala in the North West province; and Sedibeng in Gauteng province. The intervention will be delivered by LHWs and three district coordinators who will each cover 1–2 clinics.

This is a pragmatic parallel superiority individually randomised controlled trial. There are two treatment arms:

The control arm (Arm1): Intervention arm – participants will receive the PROLIFE programme;

The intervention arm (Arm2): Control arm – participants will receive usual treatment and support provided to TB patients in TB treatment clinics in South Africa ('usual care').

Full details of the background and design of the trial are presented in the protocol (version 1.2 Prolife Protocol_15 Dec 17_with markup) and the published protocol in Moriarty et al (2019) https://doi.org/10.1186/s13063-019-3551-9.

Participants

The inclusion criteria for participants are:

- adult patients (aged ≥ 18 years)
    - with drug-sensitive (bacteriologically or clinically confirmed) PTB;
- initiating TB treatment or on TB treatment for < 1 month (these include both 'new' and 'retreatment' patients);
- current smokers and/or
- hazardous/harmful drinkers who are not alcohol dependent (Alcohol Use Disorders Identification Test [AUDIT] score ≥ 8 for men or ≥ 7 for women but < 20);
- access to a functional mobile phone; and
- understand one of the four languages used for the trial (Sesotho, Setswana, Isizulu or English).

Exclusion criteria:

- alcohol-dependent participants (AUDIT score ≥ 20);
- Extrapulmonary TB without PTB; or
- Resistance to one or more TB drugs at baseline

4. Sample Size

We will recruit 696 participants (348 per study arm). The sample size calculations were based on the following assumptions:

- Detection a 10% difference in TB treatment success rates (0.86 vs 0.76) in the ProLife group versus the control group
- 80% power,
- a significance level of 0.05, and
- 25% attrition.

The sample size per clinic was in the range of 14–74 participants per clinic with a median of 24. The assumed success rates in the control group are based on actual success rates in TB patients in the studied provinces that were available at the time of sample size calculations in 2015.

5. Randomisation

Patients will be randomised using a randomised sequence generator performed by the trial statistician (MK) who will remain blind to the arm allocation. We will use block randomisation with varying block sizes stratified by the clinic to achieve equal numbers in intervention and control groups within each clinic. Allocation concealment will be done with consecutively numbered, sealed, opaque envelopes.

Lay health workers delivering the intervention, field researchers, and participants cannot be blinded to the intervention. However, the determination of the primary outcome will be completed by TB nurses who are blinded to the intervention status of the participants based on routinely collected data.

The statistician will be blinded to the intervention or control arm allocation of participants during the analysis stage.

6. Outcomes

6.1 Primary outcome

The primary outcome is TB treatment success at six to nine months of follow-up. This is a binary variable defined as

- Success: cured or treatment completed
- Failure: failed treatment, death, acquired drug resistance, loss to follow-up or 'default', or not outcome evaluated.

The different mutually exclusive treatment outcomes are summarised here

Treatment outcome	**Definition**
Cure	Patient in whom baseline smear or culture was positive at beginning of treatment AND is smear/culture negative in the last month of treatment and on at least one previous occasion at least 30 days prior According to local protocol, a patient who is diagnosed using Gene Xpert and is sputum negative for TB at 11 and 23 weeks is considered 'Cured'.
Treatment completed	Patient whose baseline smear or culture was positive at the beginning and has completed treatment but does not have a negative smear/culture in the last month of treatment and on at least one previous occasion > 30 days prior. Patients diagnosed with PTB whose baseline smear (or culture) result was negative and who started treatment based on clinical and radiological findings who have shown clinical improvement and completed the prescribed course of treatment. *N.B. The smear examination may not have been done or the results may not be available at the end of treatment.*
Treatment failure	Patient whose baseline smear or culture was positive and remains or becomes positive again at 5 months or later during treatment. Patients who were negative at baseline but were later found to be positive. *N.B. This definition excludes those patients who are diagnosed with RR-TB or MDR-TB during treatment.*
Died	Patient who dies for any reason during the course of TB treatment.
Treatment default	Patient whose treatment was interrupted for two consecutive months or more during the treatment period.
Transfer out	Patient who was referred to a facility in another district to continue treatment and for whom the treatment outcome is not known.
Acquired resistance	Participants who are subsequently referred for MDR treatment.

6.2 Secondary outcomes

The following outcome measures will be recorded at the six-month follow-up:

- sputum conversion at the end of treatment in the group of participants who had bacteriology confirmed PTB at baseline [1]
- continuous smoking abstinence for identified smokers at baseline[2]

Whereas, the following will be assessed at three and six months follow-up:

- reduction in harmful or hazardous drinking[3]
- TB and ART medication adherence will be measured using a modified version of the AIDS Clinical Trials Group (ACTG) Adherence Questionnaire[4]; using an adherence index calculated by the formula (using the four-day recall table):

  [Total number of doses taken/Total number of doses prescribed] x 100

  Patients with at least 95% of adherence will be considered as having optimal adherence otherwise will be considered as having low (or suboptimal) adherence.
- increase in proportion of HIV-positive participants on ART at three and six months from baseline using standardised questions on the CRF.

6.2.1 Monitoring adverse events

Adverse events (AE) and serious adverse events (SAE) will be defined *apriori* and relevant information will be collected.

A **Serious Adverse Event (SAE)** is actually a special case of an adverse event where adverse outcomes are severe. It includes following events: Death of any of the participants associated with a clinical trial. **Examples of events**: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant.

An **adverse event (AE)** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

The events are reported to ethics committee within 72 hours

[1] i.e. cure rates in intervention group versus control group for participants who initially had sputum AFB-positive, culture-positive or GeneXpert-positive PTB

[2] defined as a self-report of not smoking > 5 cigarettes six months from the start of the abstinence period, supported by a negative biochemical test CO < 7 ppm

[3] alcohol use will be measured using the AUDIT questionnaire. The questionnaire will be administered at screening (which will take place on the same day or shortly after the baseline assessment) and again at three months and six months.

[4] The questionnaire is a validated tool for measuring adherence specifically to ART and we will use an adapted version to also measure TB medication adherence [40].

The following information were collected to report the events:

Participants identification number, Gender, Age, Date of Enrollment, Arm (Control or intervention), Date of death notification to staff, Date of death , If death is related or not related to study.

6.3 Trial assessment schedule

Table 2 details the trial assessment schedule

Table 2: *Trial assessment schedule*

Assessment	*Items*	Pre randomisation	Timeline (post randomisation)				
		Eligibility (Day 0)	*Baseline (Day 0)*	*2 months*	*3 months*	*6-9 months*	*Trial end*
ELIGIBILITY							
Smoking status		X					
Smoking profile			X				
Alcohol profile		X					
Medical eligibility		X					
Eligible, consenting		X					
MEASURES							
Trial ID, visit date			X				
Socio-demographic history			X				
Depression screen			X		X	X	
Clinical review of TB Treatment record for disease information			X				X
Smoking history			X				
Smoking abstinence (self-report)					X	X	
Exhaled CO					X	X	
Record sputum culture or smear or Gene Expert result			X	X	X	X	
HIV Status			X				
ART Status (if HIV positive)			X		X	X	
AUDIT		X			X	X	
Modified ACTG (Follow up)					X	X	
Economic evaluation			X		X	X	

6.4 Other important information

In addition to the above, the following information was collected at baseline. Socio-demographic history included age, gender, marital status, education, employment status, and comorbidities. For details about these variables, see Table 3.

6.5 Fidelity of the intervention

The main fidelity analysis will be published somewhere else. Some descriptive statistics regarding fidelity will be added here once the main analysis is completed and the statistician is unblinded to the treatment arm.

7. Data

7.1 Data collection methods

The fieldworkers will screen all TB patients for eligibility immediately after the TB nurse at the clinic has initiated TB treatment and opened the TB "blue card". Consent will be obtained for this screening phase as the alcohol related questions are sensitive and the fieldworkers must gain insight in the patient files.

Eligible and consenting patients will be enrolled in the trial and the baseline questionnaire and record review completed. Patients will be given a unique Trial Number that will be used on all research documents. Data will be collected and recorded by field workers equipped with Android phones with a mobile data collection application installed.

Participants in the control arm will continue with the routine TB care. Intervention arm study participants will be referred by the fieldworker to the lay counsellor for motivational interviewing. The first MI session will be on the same day of the completion of the screening questionnaire, where possible (with a 2-week window period). The second and third MI session will be scheduled 4 weeks and 8 weeks from the first counselling session respectively each time with a 2-week window period.

MI counselling and data collection will take place in a well-ventilated private area inside or outside the clinic, and audio-recorded after consent obtained. Fieldworkers and LHWs will be provided with high particulate respirator masks to minimise the risk of infection.

Fieldworkers will follow-up all participants in both arms at 3 and 6 months within a window period of 2-weeks before and 2-weeks after the ideal 3 and 6-month visit. Participants will receive SMS reminders 3 days before each planned visit. Participants will also be in a position to send "please call me "messages to the fieldworkers or district coordinators, who will then call the participant to solve problems that may have arisen with the appointment.

Patients who did not return for the planned 3 and 6 months visit will be contacted by telephone up to 3-times, as needed. Home visits will also be undertaken by existing clinic "tracer teams" or Community Based Outreach teams -where feasible - for participants who cannot be traced by telephone. The data collection process is illustrated in Table 3.

Table 3: Data Collection Process by time-point and details of data collection method		
Time-point	**Information required at time-point**	**Data collection method**
Baseline interview	**1. <u>Socioeconomic and demographic status (to include history of mine work)</u>** ● Age ● Gender ● Marital status ● Educational level achieved ● Employment ● Mine work/type of mine work 2. Clinical information: ● Patient category (First episode vs recurrence) ● Site of disease ● Results of sputum smear, culture and Gene Xpert ● HIV status ● ART information ● Co-morbidities 3. Current smoking status and quit history, second hand smoke exposure 4. Alcohol history 5. Depression	TB Treatment Record CRF – Questions to participant – demographic details CRF – Questions to participant and information from the TB Treatment Record (as indicated in CRF) Questions adapted from Global Adult Tobacco Survey Questionnaire Baseline AUDIT score CES-D
3 months	1. ART information 2. TB and ART medication adherence (modified ACTCG) 3. Alcohol history (repeat AUDIT) 4. Smoking history 5. SLT use	CRF – Question to patient ACTG questionnaire for both TB medication and ART AUDIT score at 3 month

	6. Depression	Follow-up questions as per Russell's Standard and exhaled CO CES-D
6 months	1. TB treatment status (Primary outcome) 2. Sputum smear or culture result 3. ART information 4. TB and ART medication adherence 5. Alcohol history (repeat AUDIT) 6. Smoking history and exhaled CO 7. Depression	TB treatment outcome from TB Treatment Record combined with information from TB record on cultures and smear results. CRF- Question to patient Follow-up ACTG questionnaire at 6 months AUDIT at 6 months Questions as per Russell's Standard and exhaled CO CES-D

7.2 Data management

Sefako Makgatho University (SMU) appointed a data manager who will utilise an electronic platform for data collection, ensuring data quality, and facilitating the SMS messages.

Fieldworkers collecting research data will be equipped with Android mobile phones, which will have a mobile application installed on them to allow for data collection in areas with poor internet connectivity. The electronic data captured will be stored on secure and password protected storage servers and mobile phones, which ensure data privacy through only allowing authorised research staff access to the data.

The electronic data collection system used for the study requires an SMS gateway to send and receive messages to the research participants. Consenting participants' phone numbers, participant IDs, and associated SMS messages will be stored on the SMS gateway's secured and password-protected server.

Data quality will be ensured by providing fieldworkers with standard operating procedures (SOPs), training, and ongoing support on the importance of data quality, data collection, and data collection problem-solving. The data manager will continuously monitor the captured data for missing variables and inconsistencies in order to resolve any data problems.

The data manager will export the data from the secured server, conceal the participants study arm allocation, and de-identify the data before sharing the data in STATA and R compatible formats. The exported de-identified data will be stored in Dropbox, a secure cloud storage platform, for sharing with the lead trial statistician at the University of York for analysis.

All research data and documents referring to the PROLIFE trial will be stored and maintained in a secured storage space at SMU for a minimum of 15 years from the end of the PROLIFE trial. Study materials will be destroyed 15 years after the study.

8. Analysis

The computer packages STATA 16 (StataCorp. 2019) and R 3.5.3 (ref) will be used. Significance tests will be two-sided and the significance level is set at 0.05. The statistician will remain blind to allocation until results are finalised. We will follow the CONSORT statement guidelines in reporting.

Below, we detail the analyses that we will carry out for the data collected at baseline, the primary outcome, the secondary outcomes, and adverse events. We also list the sensitivity analyses that we might perform and subgroup analyses.

8.1 Participants Flow

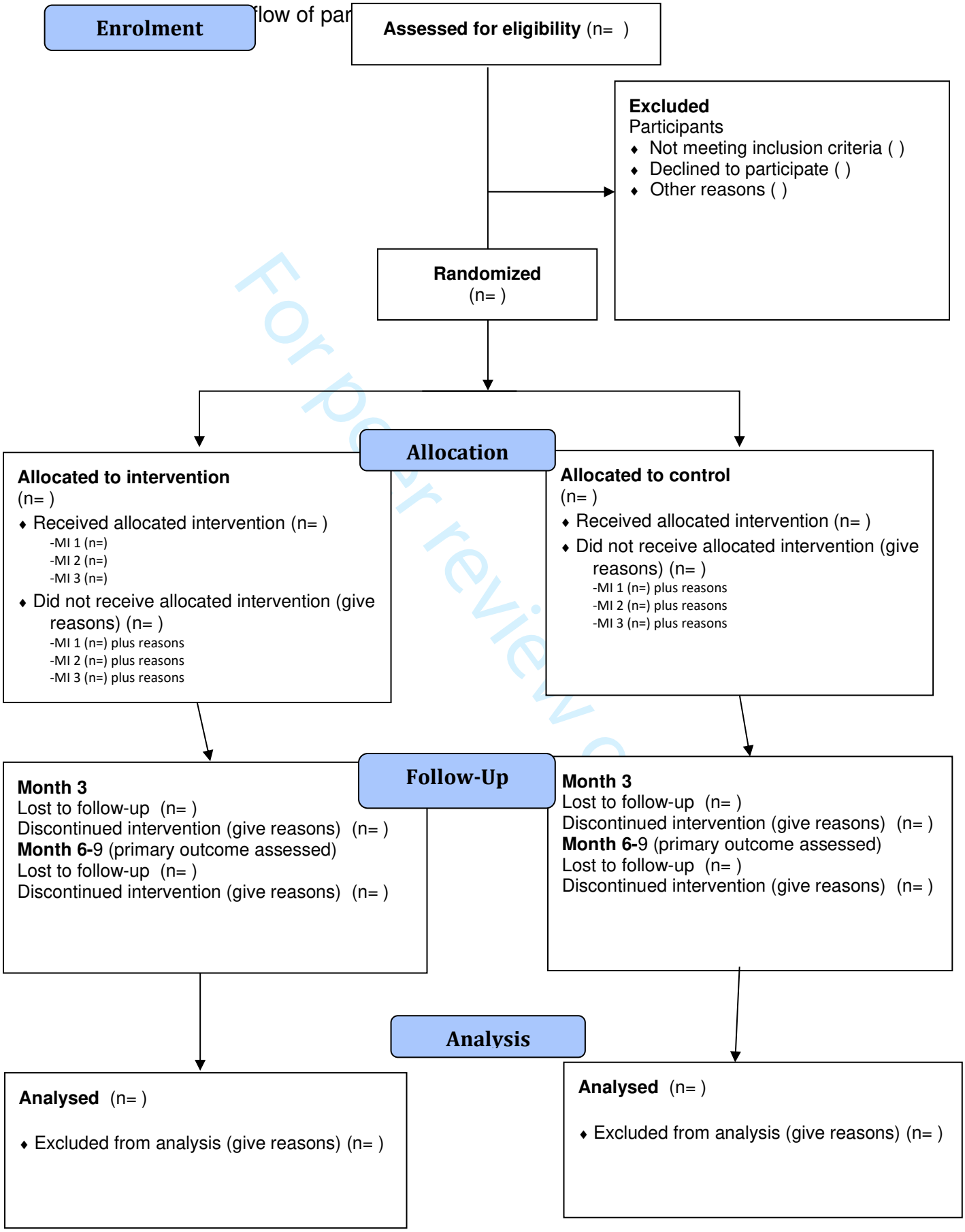


Figure 1 CONSORT DIAGRAM SHOWING FLOW OF PARTICIPANTS

8.2 Baseline data

Baseline data Analysis Plan:

Baseline data including demographic variables will be summarised descriptively by trial arm, but no formal statistical comparisons will be undertaken. Continuous measures will be reported as means and standard deviations (SD) while categorical data will be reported as counts and percentages, see Tables 1 to 4 in Appendix A. For skewed continuous measures, we will also provide medians and interquartile ranges.

Baseline data results:

Consent:

In the control arm (Arm1) 286 gave written consent and 5 verbal consent for participation in the study and for access to their medical records
In the intervention arm (Arm2) 279 gave written consent and 4 verbal consent for participation in the study and for access to their medical records

Baseline Imbalances

Education:

It seems that for education there is imbalance between the two arms for Grades 8-11/Grade 12/Higher; the control arm (Arm1) had a higher educated group the difference in percentage points 8.2% as opposed to 2.8% in the intervention arm, see Table 2 for further details. There are 9 participants who are not literate in the study (7 in the control arm (Arm1) and 5 in the intervention arm (Arm2)).

Drinking

In the intervention arm, 223 (78.8%) had a drink in the past 12-months compared to 208 (71.5%) in the control arm, see Table 3.
In the control arm (Arm1), 110 (37.8%) were drinkers only, 83 (28.5%) were smokers only, and 98 (33.7%) were smokers and drinkers compared to 92 (32.5%), 60 (21.2%), and 131 (46.3%) in the intervention arm (Arm2), respectively.

Assets:

The vast majority had a radio (84%), a television (89%), a refrigerator (85%), an electric or gas stove (86%), and a microwave (67%), however, only 50% had a washing machine. Furthermore, a minority had a landline telephone (7.5%), a desktop or laptop computer (20%:), and a vacuum cleaner or floor polisher (15%). Figure 2 is a boxplot of the total number of assets by study arm. The spread in the control arm (Arm1) is greater than that in the intervention arm (Arm2). However, the mean number of assets is similar across the two groups of 5 (SD: 1.87).

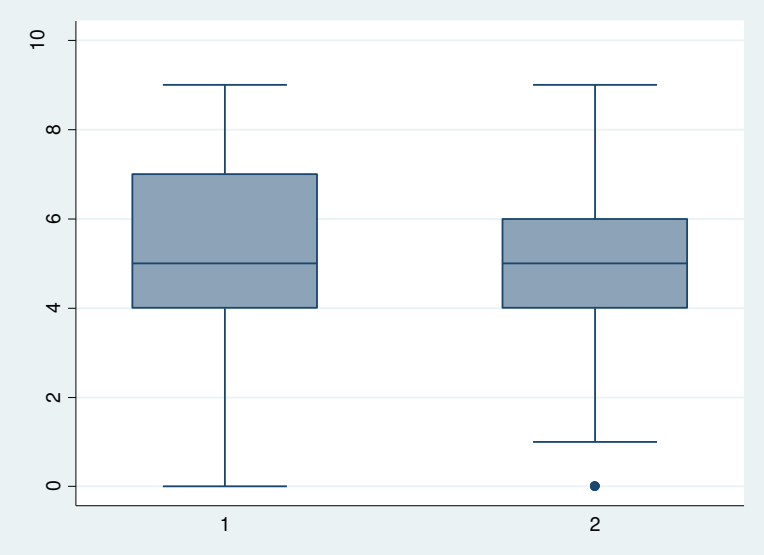


Figure 2: A boxplot of the total number of assets by study arm

Medical History:

There were 305 (53.2%) **HIV positive** participants out of which 204 (65.38%) were using Cotrimoxazole and 257 (82.37%) were undergoing anti-retroviral therapy, see Table 2.

TB History: The vast majority of participants were New TB patients 513(91.3%), with Pulmonary only (ICD-10 A15) being the site of disease for the vast majority 553 (98.9%). Among those with results known, the majority had one pre-treatment smear result 366 (89.9%), one Gene XPert recorded 435 (97.5%), and one culture result recorded 96 (96%).

Among those with results available, 220 (58.51%) had at least **one positive smear** result,362 (87.23%) had at least **one positive Gene XPert result**, and 35 (47.95%) at least **one positive culture result**.

However, 85 (53.46%) in the control arm had at least one positive smear result within 60 days of the TB treatment start date compared to 96 (61.15%) in the intervention arm.

In addition, only 34 had their culture results within 60 days from the TB start dates of which 21 had positive results; 11 in the control arm compared to 10 in the intervention arm.

The vast majority of participants did not have any **co-morbidities** 525 (96.3%) and 18 (3.3%) had one.

Baseline Smoking Related variables:

Thirty five percent (202) did not smoke in the past month, whereas 52% smoked daily and the remaining 13% smoked in the past month but less frequently than on a daily basis, see Table 3.

In the past 30 days, the vast majority were exposed to smoke for seven days or less at: home 462 (80.5%); cafes/restaurants 464 (80.8%); Shebeens, bars or clubs 432 (75.3%); Bus/train/taxi/ vehicle 448 (78.0%); and Shops/shopping mall 461 (80.3%) and where applicable at the workplace 173 (66.8%).

Among those who smoked in the past month 372: 181 in the control arm (Arm1) vs 191 in the intervention arm (Arm2),

345 (92.7%) **smoked manufactured cigarettes** of which 225(65%) did so on a daily basis in the past seven days whereas 40 (11.6%) did not smoke in the past week. The mean number of days smoked was 5.42 days in the past week (SD: 2.49) with 6.34 cigarettes (SD: 7.39) smoked daily on average.

Hand-Rolled cigarettes were used by 35 participants of which 16 (45.7%) smoked daily in the past week. They smoked on average for 4.11 (SD:2.91) days in the past week and on average smoked 3.77 (SD: 3.27) hand-rolled cigarettes per day.

There was only one person who exclusively smoked waterpipe, two who exclusively smoked pipe, and seven who exclusively used other formats of tobacco other than the ones that are listed here.

For the vast majority the total number of cigarettes smoked is based on their answer to manufactured cigarettes. In 27 cases, they supplemented this with other sources and 8 used only other forms to report the number smoked on average per day.

Over the past 3 months, they **spent** on average 174.58 (SD: 181.61) Rands per week on tobacco products.

Smoking restrictions

No smoking was allowed **inside home** for 204(54.8%) participants, whereas 119(32.0%) had some rule where/when it is allowed and 49(13.2%) had no rules in place.

Quit Attempts:

Among smokers, 116 (31.2%) made an **attempt to quit**; the mean number of attempts to quit was 2.56 (SD: 2.32).

Furthermore, 213 (57.3%) said they will probably **try to quit** smoking completely and permanently in the next three months and 126 (33.9%) said that they definitely will.

Whereas, 207 (55.6%) said they will probably **quit** smoking completely and permanently in the next three months and 130 (34.9%) said that they definitely will.

Only 39 (10.5%) have ever used any methods in the past 3 months to help them stop smoking tobacco. These spent on average 136.64 (SD: 205.36) Rands on methods to help you stop smoking in the past 3 months.

Smokeless tobacco was used by only 24 participants (4.2%). They have been using ST for an average of 10.5 years (SD: 8.8) and have started using it at the age of 27 (SD: 11.33) years on average.

Heaviness of smoking:

In the control arm (Arm1), 67(37.0%) of smokers reported smoking within 5 minutes of waking up whereas 82(42.9%) did so in the intervention arm (Arm2).

Among those who smoked and who reported the number of cigarettes/pipes/cigars they used on average per day, 134(74.03%) in the control arm (Arm1) and 158(82.72%) in the intervention arm (Arm2) were considered as heavy smokers.

8.3 Primary analysis

8.3.1 Primary outcome definition:

As per section 6.1, we would define the primary outcome as those who had a successful treatment versus not. Where successful treatment is considered if the patient is considered to have been cured or treatment completed; all other categories will be deemed as not successful. The successful treatment[5] categories are defined as follows:

Cure	Patient in whom baseline smear or culture was positive at beginning of treatment AND is smear/culture negative in the last month of treatment and on at least one previous occasion at least 30 days prior According to local protocol, a patient who is diagnosed using Gene Xpert and is sputum negative for TB at 11 and 23 weeks is considered 'Cured'.
Treatment completed	Patient whose baseline smear or culture was positive at the beginning and has completed treatment but does not have a negative smear/culture in the last month of treatment and on at least one previous occasion > 30 days prior. Patients diagnosed with PTB whose baseline smear (or culture) result was negative and who started treatment based on clinical and radiological findings who have shown clinical improvement and completed the prescribed course of treatment. *N.B. The smear examination may not have been done or the results may not be available at the end of treatment.*

8.3.2 Primary outcome Analysis

For the primary outcome, we will conduct analysis on an intention-to-treat basis. We will use binary logistic regression to compare the main outcome between the

[5] Following discussion with the team, we will take this at face value as it is not possible to query some of the anomalies found in the recording of dates of tests.

intervention and the usual care arm. We will also investigate any potential clustering at the centre level and account for it. We will present the results for this analysis in Table 6.

We will also adjust for HIV status, sex, alcohol versus tobacco versus both, and district; if these differ between trial arms at baseline.

8.3.3 Primary outcome Analysis Results

Table 4 gives the descriptive statistics for the initial outcome and the derived - dichotomised outcome; these indicate that overall, 69% were classified as successful treatment based on the medical professional assessment (cured/treatment completed). This percentage was similar for the two arms with the control arm (Arm1) having a slightly higher percentage of success of 70.1% compared to 67.8% in the intervention arm (Arm2)[6]. Table 9 gives the distribution per centre by study arm. Generally, these are fairly balanced any imbalance observed is most probably due to the early termination of the study.

For 203 participants, the TB treatment outcome date was not available, with those participants more likely to not have been cured (59% not cured), however, the percentage was similar across the two study arms for those with missing TB treatment outcome date.

The odds of successful treatment is 0.9 (95% CI: (0.64,1.27)) in the intervention arm (Arm2) compared to the control arm (Arm1). This estimate is very similar to the estimate adjusting for district and drinking/smoking status. This is also the case if you further adjust for sex and HIV status at baseline where the OR is 0.86 (95% CI: (0.60,1.24)); see Table 6 for further details.

[6] Primary outcome Control: 204/291, 95% CI proportion 0.70 (0.64,0.75)
Primary outcome Intervention:192/283, 95% CI proportion 0.68 (0.62,0.73)

8.4 Secondary analyses

Secondary analyses plan

In the group of participants who had bacteriology confirmed at baseline, we will use logistic regression to compare cured versus not cured, as indicated by the outcome at the end of treatment, between the two study arms. We will also control for baseline characteristics and other covariates such as sex, alcohol use, HIV-status, district, and account for any potential clustering by centre.

We will use a similar approach for the six-months continuous smoking abstinence outcome. This analysis will be performed on the group of participants who were current tobacco smokers at baseline. We will also control for baseline characteristics and other covariates such as age, duration of smoking, alcohol problem (hazardous, harmful, non-drinker/light drinker), heaviness of smoking index[7], depression, and potentially HIV-status.

For the reduction in harmful or hazardous drinking, we will use linear regression to measure difference in total AUDIT score between control and intervention groups accounting for the baseline AUDIT scores. Separate analyses for the AUDIT at 3 and 6 months will be performed.

The AUDIT is a 10-items questionnaire with a range between 0 and 40 where higher values indicate higher dependency.[8] It is worth mentioning that a score of 8 or more

[7] [Goedele's Comment on an earlier Version]Definitely a measure of severity of smoking and duration of smoking. For example Heaviness of Smoking Index which can be derived as follows:

HSI=Heaviness of smoking index ≥ 4, calculated based on sum of time to first cigarette (0: 61+min, 1:31-60 min, 2: 6-30 min, 3: ≤5 min) and number of cigarettes smoked per day (0: 0-10 cigarettes per day [CPD]

Also: age, duration of smoking, alcohol problem (hazardous, harmful, non-drinker/light drinker), maybe HIV-status, (adding this may reduce your sample size too much, because of missing HIV-status, unless you include HIVstatus unknown as a category of HIV-status). Depression

[8] Scoring the audit
Scores for each question range from 0 to 4, with the first response for each question (eg never) scoring 0, the second (eg less than monthly) scoring 1, the third (eg monthly) scoring 2, the fourth (eg weekly) scoring 3, and the last response (eg. daily or almost daily) scoring 4. For questions 9 and 10, which only have three responses, the scoring is 0, 2 and 4 (from left to right).
A score of 8 or more is associated with harmful or hazardous drinking, a score of 13 or more in women, and 15 or more in men, is likely to indicate alcohol dependence.

is associated with harmful or hazardous drinking, a score of 13 or more in women, and 15 or more in men, is likely to indicate alcohol dependence. Eligibility criteria for our study is an AUDIT score ≥ 8 for men or ≥ 7 for women but <20. However, if assumptions of linear regression are not met we will either transform the data or use alternative regression analyses such as ordinal logistic regression.

Adherence to TB and ART medication will be measured using an adherence index based on a modified version of the AIDS Clinical Trials Group (ACTG) Adherence Questionnaire; where patients with at least 95% of adherence will be considered as having optimal adherence otherwise will be considered as having low (or suboptimal) adherence. We will use logistic regression to model patient's characteristics (age, sex, alcohol, smoking status, depression) that might influence adherence at 6-month; we will also compare adherence between study arms. Similar to the previous outcomes, we will account for any potential clustering by centre.

We will also report the proportion of HIV-positive participants on ART at six months and compare these to the baseline using standardised questions on the CRF.

8.4.1 Secondary outcome definitions that involve defining a positive baseline test:

To operationalise the above we need to define how we determine if someone has a positive baseline smear or culture. Each participant might have up to two tests of the following: smear test, GeneExpert test, and culture test.

If a test was administered two times then to be considered negative both tests should be negative, otherwise it is considered positive. If a test was administered only once, then the result of that instance is taken as is.

1Saunders JB, Aasland OG, Babor TF et al. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption — II. Addiction 1993, 88: 791–803

If for a patient more than one test was administered, then to be considered negative the result should be negative under both tests.

This is illustrated in the following table.

Baseline	P=+, N = -		
		XXXX Test at run 2 (Result 2)	
XXXX Test run 1 (Result 1)		N	P
	N	NN	NP
	P	PN	PP
XXXX=Smear or Culture or GeneXpert			
Smear test at baseline	N1	NN	
	P1	NP, PN, PP	
Genexpert	N2	NN	
	P2	NP, PN, PP	
culture	N3	NN	
	P3	NP, PN, PP	
Positive at baseline	PB	P1 or P2 or P3	
Negative at baseline	NB	N1 and N2 and N3	

To define a conversion among those who were positive at baseline, we used the primary outcome response category cured to indicate a negative result at month 6 per the nurse's assessment.

Among the 403 participants who were positive at baseline 168(41.69%) were recorded as cured by 6-month of these 83 (39.9%) in the control arm compared to 85 (43.59%) see Table 4. The odds ratio of conversion is 1.16 (95% CI: (0.83,1.63)) comparing the intervention arm to the control arm. When adjusting for district, sex, and smoking/drinking status and HIV status at baseline, the OR reduces to 1.07 (95% CI: (0.76,1.51))

8.4.2 6-months Continuous Abstinence

For this outcome, those who smoked cigarettes at baseline were considered as the analytic sample. In addition, those where the following could not be ascertained: self-report of not smoking > 5 cigarettes six months from the start of the abstinence period and supported by a negative biochemical test CO < 7 ppm were considered as smokers for the analysis of this variable. The number of participants who identified as cigarette smokers at baseline were 345 (60.1%)[9].

23 (85.19%) out of 27 with three measurements available[10] managed to abstain continuously for six months. These were similarly distributed across the two study arms, see Table 4. Among those who identified as cigarette smokers, 10 (5.59%) participants in the intervention arm continuously abstained. In the control arm there were 12 (7.23%) who continuously abstained for 6-months.

The crude odds of 6-months continuous abstinence is 0.76 (95% CI: (0.35,1.63)) in the intervention arm compared to the control arm among baseline cigarette smokers. Given the limited number of those who were identified as continually abstained, we were only able to adjust for one additional variable at a time. Adding one of the following variables: heaviness of smoking, type of drinker at baseline, age when started smoking, and the duration of smoking at baseline, the adjusted odds ratio of continuous abstinence comparing the intervention to the control arm did not differ much from the crude estimate of 0.76. The adjusted estimate for the various models ranged between 0.73 and 0.76 with similar confidence limits as for the crude estimate. Furthermore, we did not have evidence that any of the adjusting variables were statistically significantly correlated to continuous abstinence in these models.

We carried an additional analysis where those who died and were smokers at baseline, 22 in total, 20 were cigarette smokers and were removed from the analytical sample for the continuous abstinence outcome. This resulted in a crude

[9] Any type of tobacco smoking at baseline 372 (64.8%). The numbers reflect those who used manufactured cigarettes which were the vast majority.

[10] We had only 27 participants who had self-report of not smoking at 3 months, 6 months and a carbon monoxide reading at 6 months. Continuous abstinence was defined as a self-report of not smoking > 5 cigarettes six months from the start of the abstinence period and supported by a negative biochemical test CO < 7 ppm

OR of 0.78 which is similar to the OR when the larger analytic sample was considered; this was also the case for the associated 95% CI. Similar estimates were observed when adjusting for the aforementioned variables.

We carried an additional analysis where the analytic sample was all those who were smokers regardless of the type used. There were a total of 372 that identified as smokers. The crude odds ratio in this case changes to 0.86 (95% CI: (0.38,1.95)). The 95% CI is similar to that of the smaller analytic sample. When adjusting for the heaviness of smoking, type of drinker at baseline, age when started smoking, and the duration of smoking at baseline, the adjusted odds ratio of continuous abstinence comparing the intervention to the control arm did not differ much from the crude estimate.

3-months Continuous Abstinence

Among those who identified as cigarette smokers, 20 (11.17%) participants in the intervention arm continuously abstained for 3-months while in the control arm there were 27 (16.27%) who continuously abstained for 3-months.

The crude odds of 3-months continuous abstinence is 0.65 (95% CI: (0.37,1.14)) in the intervention arm compared to the control arm among baseline cigarette smokers. Given the limited number of those who were identified as continually abstained, we were only able to adjust for one additional variable at a time. Adding one of the following variables: heaviness of smoking, type of drinker at baseline, age when started smoking, and the duration of smoking at baseline, the adjusted odds ratio of continuous abstinence comparing the intervention to the control arm did not differ much from the crude estimate of 0.65. The adjusted estimate for the various models ranged between 0.63 and 0.66 with similar confidence limits as for the crude estimate.

Point Abstinence

There were 57 participants who indicated that they stopped smoking tobacco completely at the 3-month follow-up, of which one had more than 5 cigarettes in the past 3 months. There were 81 participants who indicated that they stopped smoking tobacco completely at the 6-month follow-up, of which three had more than 5 cigarettes in the past 3 months. Only 30 participants had information for the entirety of the 6-month period, of which none consumed more than 5 cigarettes over the past 6-month period. Of these, 23 had a confirmed CO < 7 ppm, 4 had these levels >= 7, and 3 were missing.

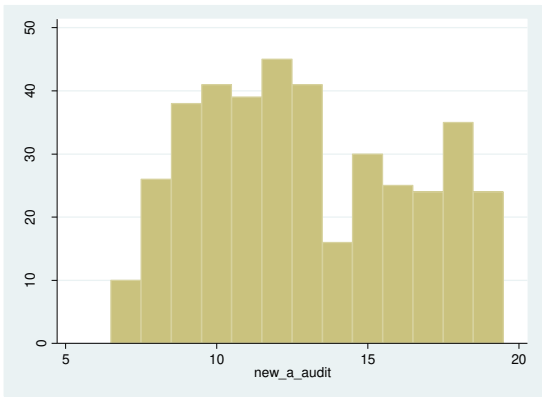
182 responded that they continued smoking either as usual or at a reduced rate but regularly at month 3; whereas 133 done so at month 6 of these we had 97 that had measurements at both time points thus resulting in a total of 218 where they have smoked on a regular basis over the past 6 month period. 11 had responded as not smoking in the past three months at month 6 but had missing information for the first three months; 9 of these had carbon monoxide readings available at month 6. Of these nine, two had their CO >= 7 (in fact these were 10 & 10.1).

8.4.4 Change in harmful or hazardous drinking at month 3 and 6 follow-ups

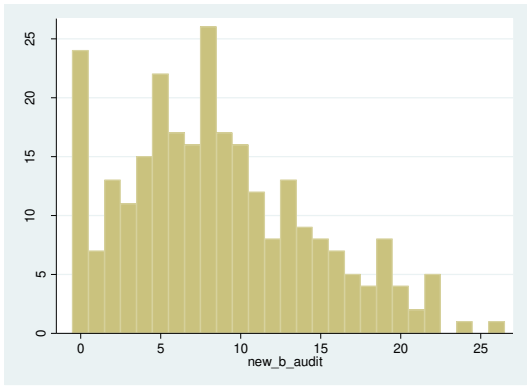
Alcohol use was measured using the AUDIT questionnaire. We will assess whether there has been a reduction in alcohol consumption three months and six months following recruitment. This analysis will be performed on the group of participants who were harmful or hazardous drinkers at baseline. Figure YYY provides histograms of the AUDIT score at baseline, 3-months and 6-months, respectively, among those who were considered as hazardous or harmful drinkers. It also presents scatterplots of the 3-months and 6-months scores versus the baseline scores for this group by trial arm, respectively.

Among those who were harmful or hazardous drinkers at baseline those in the intervention arm had on average a reduction of 0.04 points (95% CI: (-2,1.91)) on the AUDIT score at 6-months compared to those in the control arm controlling for their baseline score, see Table 6. However, when additionally adjusting for district, sex, and smoking/drinking status (which effectively flags smokers/non-smokers who are also drinkers) and HIV status at baseline; the intervention arm had an average increase of 0.02 points on the AUDIT score (95% CI: (-1.55,1.6)) compared to the control arm. It is worth noting that of the variables in the adjusted model; the only statistically significant result is for the district variable. It seems that those in district "S" score on average 5.8 points less than those in "B" (95% CI: (-11.26,-0.35)); similarly those in "L" score 5 points less than those in "B" on AUDIT but we do not have evidence that this difference is statistically significant (95% CI: (-10.35,0.26)), see Table 6 for further details.

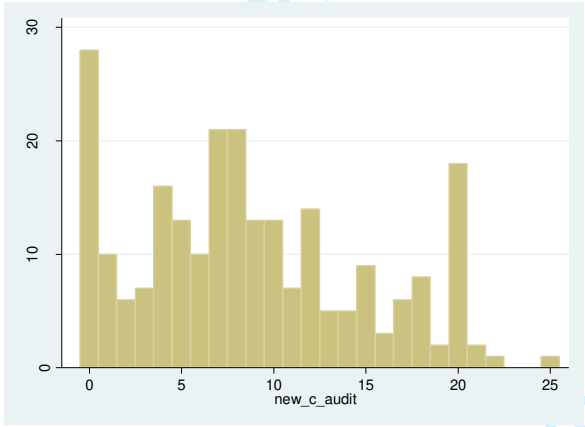
At 3-month, the estimates were an average increase of 0.55 (95% CI: (-1.01,2.11)) on the AUDIT score in the intervention arm compared to the control arm when only accounting for the baseline scores; whereas it increased to 0.74 (95% CI: (0.62,2.1)) when adjusting for other covariates in the model, for further details see Table 7.



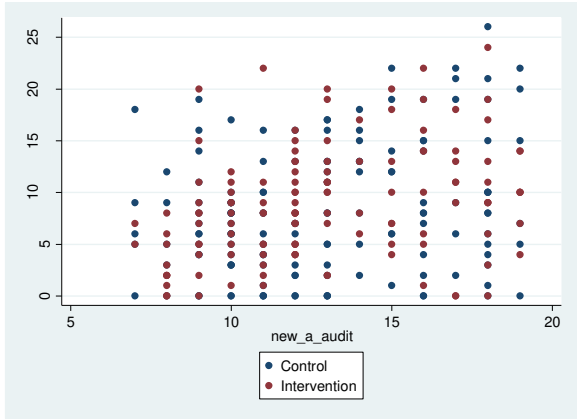
(a)



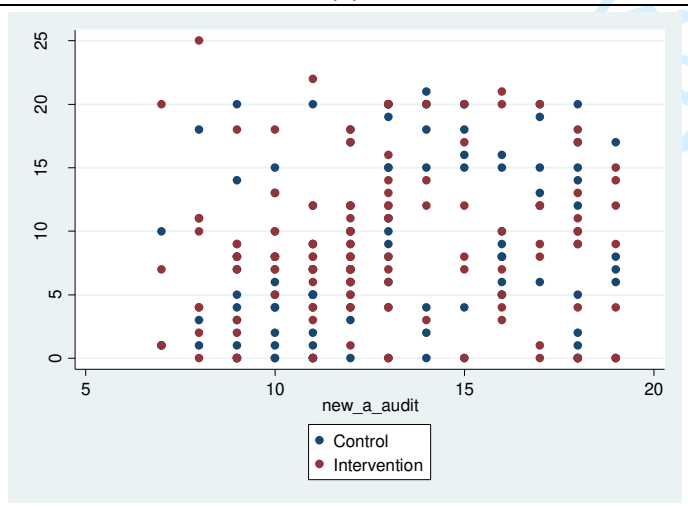
(b)



(c)



(d)



(e)

Figure YYY: Graphs (a), (b), and (c) are histograms of the AUDIT score at baseline, 3-months and 6-months, respectively, among those who were considered as hazardous or harmful drinkers. (d) and (e) are scatterplots of the 3-months and 6-months scores versus the baseline scores for this group, respectively.

8.4.5 Proportion of ART uptake of HIV-positive participants at month 3 and 6 follow-ups

We will assess whether there has been an increase in proportion of HIV-positive participants on ART at three and six months from baseline using standardised questions on the CRF.

There were 171 HIV-positive participants whose baseline ART medication status was known and whose ART medication status was known as well at 6-months. Of these, 123 remained on their medication, 19 took up medication at 6-months compared to not taking medication at baseline, whereas 29 stopped taking their medication at 6-months but were on medication at baseline, see Table 6 for further details.

There were 10 who had an unknown status in terms of medication at baseline and no information was available about them at 6-months, 12 who were initially of unknown medication status who took up medication at 6-months (these were equally distributed between the two arms). Furthermore, there were 10 who were not taking medication at baseline and 102 who were taking medication at baseline whose 6-months medication status was not recorded.

At 6-months, the odds ratio of taking medication at 6-months was 2.05 (95% CI: (0.80,5.27)) in the intervention arm compared to the control arm, controlling for ART baseline medication status.

There were 188 HIV-positive participants whose baseline ART medication status was known and whose ART medication status was known as well at 3-months. Of these, 122 remained on their medication, 16 took up medication at 3-months compared to not taking medication at baseline, whereas 50 stopped taking their medication at 3-months but were on medication at baseline, see Table 7 for further details.

There were 9 who had an unknown status in terms of medication at baseline and no information was available about them at 3-months, 11 who were initially of unknown

medication status who took up medication at 3-months, and two who were initially of unknown medication status who were not taking medication at 3-months. Furthermore, there were 9 who were not taking medication at baseline and 82 who were taking medication at baseline whose 3-months medication status was not recorded. Furthermore, there were 4 who carried on not taking medication at 3-months.

At 3-months, the odds ratio of taking medication at 6-months was 0.79 (95% CI: (0.38,1.65)) in the intervention arm compared to the control arm, controlling for ART baseline medication status.

Medicine Adherence:

At 3-months 165 (98.8%) of 167 participants had optimal ART medication adherence, whereas 139(97.2%) of 143 had optimal ART medication adherence. These were similar across the two arms.

Similarly, at 3-months 319(91.67%) of 348 participants had optimal TB medication adherence, whereas 120(90.23%) of 133 had optimal TB medication adherence. These were similar across the two arms.

8.5 Subgroup analyses (See above analyses)

We will conduct subgroup analyses to determine whether TB treatment outcomes differ between subgroups, as follows: HIV-positive versus HIV-negative participants; participants with an alcohol problem only versus smokers only versus participants who are conjoint smokers and drinkers; and participants who were GeneXpert positive versus participants who were GeneXpert negative at baseline.

8.5 Sensitivity analyses

In case of missing data, multiple imputations and appropriate sensitivity analyses will be conducted. As it is likely that more than one variable will have missing data we will use multiple imputations using chained equations (**MICE**). A minimum of 10 imputations will be performed; however, the final number of imputations will depend on the missing in the data. We will report the decisions that we make with regard to the number of imputations and the

variables we use in the imputations. We will also conduct a sensitivity analysis to explore the implications of the missing at random assumption [21p,22p].

8.6 Adverse events

Analysis of adverse events and serious AE will explore whether these differ by treatment arm using Chi-square tests.

8.7 Planned interim review and analyses

No interim analysis is planned. The main analyses will be completed after three months of the data closing.

8.8 List of Tables and Graphs

Measures of central tendency and percentages will be reported to two decimal places whereas measures of variability and p-values will be reported to three decimal places.

The following is a list of suggested tables and graphs; the templates are included in Appendix A.

TABLE 1: Numbers in the study at Baseline and follow-ups at month 3, and 6 by centre and study arm.

TABLE 2: Descriptive statistics for socio-demographic and socio-economic characteristics at baseline and as analysed by study arm. Frequencies and (percentages) are presented unless otherwise stated

TABLE 3: Descriptive statistics for smoking history, alcohol history, clinical characteristics and depression score at baseline and as analysed by study arm. Frequencies and (percentages) are presented unless otherwise stated.

TABLE 4: Descriptive statistics for primary and secondary outcomes by study arm at baseline (where available), 3 month (where available) and 6 month. Frequencies and (percentages) are presented unless otherwise stated.

TABLE 5: Number and type of adverse events at month 2, 3, and 6 by centre and study arm.

TABLE 6: Regression analysis results for the primary and secondary outcomes at 6 month. Estimates presented with corresponding 95% CI. Crude and adjusted estimates are provided.

TABLE 7: Regression analysis results for the secondary outcomes that are measured at 3 month. Estimates presented with corresponding 95% CI. Crude and adjusted estimates are provided.

9. SAP amendment log

Amendment/addition to SAP and reason for change	**New version number, name and date**
SAP completed and signed-off	*V1.0,*
Updated verion	*V1.1, May 2020*

10. Signatures of approval

Sign-off of the final approved version of the Statistical Analysis Plan by the principle investigator and trial statistician(s) (can also include Trial Manager/Co-ordinator)

Name	**Trial Role**	**Signature**	**Date**

11. References

Moriarty, A.S., Louwagie, G.M., Mdege, N.D. *et al*. ImPROving TB outcomes by modifying LIFE-style behaviours through a brief motivational intervention followed by short text messages (ProLife): study protocol for a randomised controlled trial. *Trials* **20,** 457 (2019) doi:10.1186/s13063-019-3551-9

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21p. James R Carpenter and Michael G Kenward. Missing data in clinical trials — a practical guide. Birmingham: National Health Service Co-ordinating Centre for Research Methodology, 2008.

22p. James R Carpenter, Michael G Kenward, and Ian R White. Sensitivity analysis after multiple imputation under missing at random — a weighting approach. Statistical Methods in Medical Research, 16:259–275, 2007.

StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC.

R Core Team (201?). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

12. Appendix A (Results tables)

Table 1: Numbers in the study at Baseline and follow-ups at month 3 and 6 by centre and study arm. (SEE FLOWCHART)

TABLE 1: NUMBERS IN THE STUDY AT BASELINE AND FOLLOW-UPS AT MONTH 3 AND 6 BY CENTRE AND STUDY ARM.								
Centre	Baseline		Month 3		Month 6			
	Intervention	Control	Intervention	Control	Intervention	Control		
Total								

TABLE 2: Descriptive statistics for socio-demographic, socio-economic, and clinical characteristics at baseline by study arm. Frequencies and (percentages) are presented unless otherwise stated

TABLE 2: DESCRIPTIVE STATISTICS FOR SOCIO-DEMOGRAPHIC, SOCIO-ECONOMIC, AND CLINICAL CHARACTERISTICS AT BASELINE AND AS ANALYSED BY STUDY ARM. FREQUENCIES AND (PERCENTAGES) ARE PRESENTED UNLESS OTHERWISE STATED				
		Baseline		
	N1/N2	Control	Intervention	Total
		Arm 1	Arm 2	
Age in years: mean (SD)	291/283	39.37 (12.60)	38.56 (11.15)	
Age in years: median (IQR)				
Gender				
Female		69 (23.7)	60 (21.2)	129 (22.5)
Male		222 (76.3)	223 (78.8)	445 (77.5)
Do not want to disclose				
Marital status				
Married or living together		102 (35.1)	95 (33.6)	197 (34.3)
Divorced/separated		20 (6.9)	18 (6.4)	38 (6.6)
Widowed		10 (3.4)	7 (2.5)	17 (3.0)
Never married and never lived together		144 (49.5)	150 (53.0)	294 (51.2)
Declined to answer		15 (5.2)	13 (4.6)	28 (4.9)
Education				
No education		7 (2.4)	5 (1.8)	12 (2.1)
Grades 1-5		23 (7.9)	20 (7.1)	43 (7.5)
Grades 6-7		32 (11.0)	35 (12.4)	67 (11.7)

Grades 8-11		96 (33.0)	128 (45.2)	224 (39.0)
Grade 12		87 (29.9)	70 (24.7)	157 (27.4)
Higher		24 (8.2)	8 (2.8)	32 (5.6)
Declined to answer		22 (7.6)	17 (6.0)	39 (6.8)
Employment				
Self-employed (full-time)		30 (10.3)	36 (12.7)	66 (11.5)
Employed full-time (30 hrs a week or more)		62 (21.3)	54 (19.1)	116 (20.2)
Employed part-time (less than 30 hrs a week)		19 (6.5)	29 (10.2)	48 (8.4)
Retired		17 (5.8)	16 (5.7)	33 (5.7)
Unemployed (but able to work)		125 (43.0)	120 (42.4)	245 (42.7)
Unable to work because of long-term disability or ill health		9 (3.1)	8 (2.8)	17 (3.0)
Full-time student		12 (4.1)	4 (1.4)	16 (2.8)
Caring from my home and family/doing household work/housewife		0 (0.0)	2 (0.7)	2 (0.3)
Occasional work (“piece job”)		17 (5.8)	12 (4.2)	29 (5.1)
Declined to answer		0 (0.0)	2 (0.7)	2 (0.3)
Ever worked or spent time in mines				
No		244 (83.8)	237 (83.7)	481 (83.8)
Yes		46 (15.8)	45 (15.9)	91 (15.9)
Socioeconomic status				

Household items (Yes is displayed)				
A radio		249 (85.6)	234 (82.7)	483 (84.1)
A television		255 (87.6)	255 (90.1)	510 (88.9)
A landline telephone		21 (7.2)	22 (7.8)	43 (7.5)
A desktop or laptop computer		67 (23.0)	48 (17.0)	115 (20.0)
A refrigerator		248 (85.2)	240 (84.8)	488 (85.0)
A vacuum cleaner or floor pol		49 (16.8)	35 (12.4)	84 (14.6)
A microwave oven		198 (68.0)	189 (66.8)	387 (67.4)
An electric or gas stove		254 (87.3)	238 (84.1)	492 (85.7)
A washing machine		153 (52.6)	136 (48.1)	289 (50.3)
Total number of assets: mean (SD)		5.14 (1.96)	4.94 (1.77)	5.04 (1.87)
In the past month, number of days you or people in the household went to bed hungry because there was no food to eat				
0 days		244 (83.8)	238 (84.1)	482 (84.0)
1-7 days		45 (15.5)	34 (12.0)	79 (13.8)
More than 7 days		2 (0.7)	9 (3.2)	11 (1.9)
Declined to answer		0 (0.0)	2 (0.7)	2 (0.3)
TB and medical history				
TB history				
Patient category				
New patient		264 (92.3)	249 (90.2)	513 (91.3)
Relapse		10 (3.5)	9 (3.3)	19 (3.4)
Re-treatment after default		9 (3.1)	14 (5.1)	23 (4.1)
Re-treatment after failure		1 (0.3)	2 (0.7)	3 (0.5)
Other		2 (0.7)	2 (0.7)	4 (0.7)
Site of disease				
Pulmonary and Extra Pulmonary (ICD-10 A17-A19)		3 (1.1)	3 (1.1)	6 (1.1)

Pulmonary only (ICD-10 A15)		281 (98.9)	272 (98.9)	553 (98.9)
Number of pre-treatment smear results				
One		197 (92.1)	169 (87.6)	366 (89.9)
Two		17 (7.9)	24 (12.4)	41 (10.1)
Smear result	N =	196	180	376
At least one positive smear result		111 (56.63)	109 (60.56)	220 (58.51)
Number of Gene XPert results recorded				
One		225 (97.8)	210 (97.2)	435 (97.5)
Two		5 (2.2)	6 (2.8)	11 (2.5)
Gene XPert result	N =	211	204	415
At least one positive Gene XPert result		184 (87.2)	178 (87.25)	362 (87.23)
Number of culture results recorded on the TB Treatment record				
One		54 (94.7)	42 (97.7)	96 (96.0)
Two		3 (5.3)	1 (2.3)	4 (4.0)
Culture result	N =	41	32	73
At least one positive culture result		20 (48.78)	15 (46.88)	35 (47.95)
Co-morbidities				
Hypertension		19 (6.93)	11 (4.1)	30 (5.54)
Diabetes		5 (1.84)	4 (1.49)	9 (1.66)
Epilepsy		3 (1.09)	4 (1.49)	7 (1.29)
Mental illness		3 (1.09)	0 (0)	3 (0.55)
Liver disease		1 (0.36)	1 (0.38)	2 (0.37)
Renal insufficiency		1 (0.36)	1 (0.38)	2 (0.37)
Allergies		2 (0.76)	0 (0)	2 (0.38)

Other		1 (0.36)	1 (0.38)	2 (0.37)
Total Number of comorbidities				
0		265 (96.0)	260 (96.7)	525 (96.3)
1		10 (3.6)	8 (3.0)	18 (3.3)
2		0 (0.0)	1 (0.4)	1 (0.2)
5		1 (0.4)	0 (0.0)	1 (0.2)
HIV status				
Negative		118 (40.7)	125 (44.2)	243 (42.4)
Positive		163 (56.2)	142 (50.2)	305 (53.2)
Unknown		9 (3.1)	16 (5.7)	25 (4.4)
HIV positive patients				
CD4 Count: mean(SD)				
Using Cotrimoxazole		104 (63.8)	100(67.11)	204 (65.38)
Using anti-retroviral		139 (85.28)	118 (79.19)	257 (82.37)

TABLE 3: Descriptive statistics for smoking history, alcohol history and depression score at baseline by study arm. Frequencies and (percentages) are presented unless otherwise stated.

TABLE 3: Descriptive statistics for smoking history, alcohol history and depression score at baseline and as analysed by study arm. Frequencies and (percentages) are presented unless otherwise stated.			
	Baseline		
	Control	Intervention	Total
	Arm 1	Arm 2	Total
In the past month, smoked tobacco			
Not at all	110 (37.8)	92 (32.5)	202 (35.2)
Daily	149 (51.2)	149 (52.7)	298 (51.9)
Less than Daily	32 (11.0)	42 (14.8)	74 (12.9)
Had a drink in the past 12-months	208 (71.5)	223 (78.8)	431 (75.1)
AUDIT Score (males): mean (SD) [max :19] [min = 8 if drinkers only]	12.27 (3.98)	13.02 (3.78)	12.66 (3.89)
AUDIT Score (females): mean (SD) [max :19] [min = 7 if drinkers only]	11.32 (4.02)	10.98 (4.02)	11.15 (4)
Drinking and Smoking Combined (Constructed)			
Drinkers Only	110 (37.8)	92 (32.5)	202 (35.2)
Smokers Only	83 (28.5)	60 (21.2)	143 (24.9)
Smokers and Drinkers	98 (33.7)	131 (46.3)	229 (39.9)

	Arm 1	Arm 2	Total
Smoking History (current smokers only)	181	191	372
On the days that you smoke, how soon after you wake up do you have your first cigarette?			
After 60 minutes	30 (16.6)	28 (14.7)	58 (15.6)
31-60 minutes	24 (13.3)	16 (8.4)	40 (10.8)
6- 30 minutes	60 (33.1)	65 (34.0)	125 (33.6)
Within 5 minutes	67 (37.0)	82 (42.9)	149 (40.1)
Duration of smoking in **months**: mean (SD)	212.09 (134.03)	224.93 (127.82)	218.68 (130.86)
Duration of smoking in **months**: median (IQR)	186 (110, 282)	206 (135, 294)	200.5 (123, 287)
Age started smoking in **years**: mean (SD)	19.2 (6.3)	19.3 (6.3)	19.3 (6.3)
Age started smoking in **years**: median (IQR)	18 (15-20)	18 (16-21)	18 (15.5-20.5)
Form of tobacco used			
Manufactured cigarettes (Yes)	**166 (91.7)**	**179 (93.7)**	**345 (92.7)**
Number of days in the past 7days you smoked: mean (SD)	5.3 (2.65)	5.53 (2.33)	5.42 (2.49)
Average number of cigarettes smoked daily: mean (SD)	6.18 (6.43)	6.48 (8.21)	6.34 (7.39)
Hand-rolled cigarettes (Yes)	**14 (7.7)**	**21 (11.0)**	**35 (9.4)**
Number of days in the past 7days you smoked: mean (SD)	4.71 (2.84)	3.71 (2.95)	4.11 (2.91)
Average number of handrolled cigarettes smoked daily: mean (SD)	3.71 (3.97)	3.81 (2.82)	3.77 (3.27)
Pipe (Yes)	**4 (2.2)**	**2 (1.0)**	**6 (1.6)**
Number of days in the past 7days you smoked: median (IQR)	1 (0, 2.5)	4.5 (2, 7)	2 (0, 3)
Average number of daily sessions: median (IQR)	1 (0, 3.5)	3 (1, 5)	1.5 (0, 5)
Length of one session (on average) in **minutes**: median (IQR)	90 (60, 107.5)	60 (30, 90)	90 (30, 90)
Cigars, cheroots or cigarillos (Yes)	1 (0.55)	0 (0)	1(0.27)

Water pipe (Yes)	3 (1.7)	2 (1.0)	5 (1.3)
Other	10 (5.5)	4 (2.1)	14 (3.8)
Heaviness of smoking index >= 4	134(74.03)	158(82.72)	292(78.49)
Smoking inside your home restrictions			
Total: Not allowed	96 (53.0)	108 (56.5)	204 (54.8)
Some rules: where/when it is allowed	61 (33.7)	58 (30.4)	119 (32.0)
No rules	24 (13.3)	25 (13.1)	49 (13.2)
Attempts to quit smoking (current smokers only) (Yes)			
Ever attempted to quit in the past			
Yes	52 (28.7)	64 (33.5)	116 (31.2)
No	129 (71.3)	127 (66.5)	256 (68.8)
Number of attempts to quit: mean (SD)	2.46 (2.98)	2.64 (1.62)	2.56 (2.32)
Time elapsed since attempt to quit last time in months: mean (SD)	36.65 (94.62)	25.13 (37.91)	30.29 (69.22)
Longest duration abstinent in previous quit attempts: mean (SD)	6.15 (13.48)	4.22 (8.9)	5.09 (11.18)
Likelihood to TRY TO QUIT smoking completely and permanently in the next three months			
definitely will not	6 (3.3)	5 (2.6)	11 (3.0)
probably will not	10 (5.5)	12 (6.3)	22 (5.9)
probably will	104 (57.5)	109 (57.1)	213 (57.3)
definitely will	61 (33.7)	65 (34.0)	126 (33.9)
	Control	Intervention	

	Arm 1	Arm 2	Total
Likelihood that I WILL QUIT smoking completely and permanently in the next three months			
definitely will not	6 (3.3)	5 (2.6)	11 (3.0)
probably will not	11 (6.1)	13 (6.8)	24 (6.5)
probably will	103 (56.9)	104 (54.5)	207 (55.6)
definitely will	61 (33.7)	69 (36.1)	130 (34.9)
Ever used any methods to help you stop smoking tobacco in the past 3 months? (Yes)	23 (12.7)	16 (8.4)	39 (10.5)
Out of your pocket spend (in Rands) on methods to help you stop smoking in the past 3 months: mean (SD)	134.87 (237.58)	139.19 (155.07)	136.64 (205.36)
Average spend per week on cigarettes over the past 3 months: mean (SD)	168.77 (178.15)	180.29 (185.27)	174.58 (181.61)
Smokeless tobacco use (all participants)			
In the past month, have you used smokeless tobacco (Snuff) on a daily basis			
Not at all	275 (94.5)	275 (97.2)	550 (95.8)
Daily	12 (4.1)	6 (2.1)	18 (3.1)
Less than Daily	4 (1.4)	2 (0.7)	6 (1.0)
Duration of using ST in months: mean(SD)	113.69 (112.7)	152 (91.16)	126.46 (105.61)
Age started using ST in **years**: mean (SD)	27.56 (10.57)	25.88 (13.43)	27 (11.33)
Form of ST used (for SLT users)			
Snuff (by mouth)	2 (12.5)	0 (0.0)	2 (8.3)
Snuff (by nose)	11 (68.8)	5 (62.5)	16 (66.7)
Chewing tobacco leaves	0(0)	0(0)	0(0)
Other	1 (6.3)	0 (0.0)	1 (4.2)
	Arm 1	Arm 2	Total

	Control	Intervention	
Tobacco smoke exposure: number of days in the past 30 days, you were in a place where someone smoked close to you (all participants?)			
Home			
7 days or less	233 (80.1)	229 (80.9)	462 (80.5)
More than 7 days	58 (19.9)	54 (19.1)	112 (19.5)
Workplace (Missing 315; probably Not Applicable)			
7 days or less	84 (65.6)	89 (67.9)	173 (66.8)
More than 7 days	44 (34.4)	42 (32.1)	86 (33.2)
Cafes/restaurants			
7 days or less	230 (79.0)	234 (82.7)	464 (80.8)
More than 7 days	61 (21.0)	49 (17.3)	110 (19.2)
Shebeens, bars or clubs			
7 days or less	219 (75.3)	213 (75.3)	432 (75.3)
More than 7 days	72 (24.7)	70 (24.7)	142 (24.7)
Bus/train/taxi/ vehicle			
7 days or less	229 (78.7)	219 (77.4)	448 (78.0)
More than 7 days	62 (21.3)	64 (22.6)	126 (22.0)
Shops/shopping mall			
7 days or less	235 (80.8)	226 (79.9)	461 (80.3)
More than 7 days	56 (19.2)	57 (20.1)	113 (19.7)
	Arm 1	Arm 2	Total

Had a drink in the past 12-months	208 (71.5)	223 (78.8)	431 (75.1)
Help to stop drinking (drinkers only)			
Ever used any methods to stop drinking alcohol in the past 3 months	21 (11.2)	22 (10.7)	43 (10.9)
Average spend in Rands per week on alcohol over the past 3 months: mean (SD)	363.76 (531.56)	337.03 (387.94)	349.79 (461.66)
Depression: CESD 10 how often you felt or behaved this way during the past week			
I was bothered by things that usually don't bother me.			
Rarely or None of the Time (Less than 1 day)	180 (61.9)	159 (56.2)	339 (59.1)
Some or a Little of the Time (1-2 days)	71 (24.4)	78 (27.6)	149 (26.0)
Occasionally or a Moderate Amount of the Time (3-4 days)	24 (8.2)	31 (11.0)	55 (9.6)
Most or All of the Time (5-7 days)	16 (5.5)	15 (5.3)	31 (5.4)
I had trouble keeping my mind on what I was doing.			
Rarely or None of the Time (Less than 1 day)	150 (51.5)	136 (48.1)	286 (49.8)
Some or a Little of the Time (1-2 days)	93 (32.0)	85 (30.0)	178 (31.0)
Occasionally or a Moderate Amount of the Time (3-4 days)	31 (10.7)	38 (13.4)	69 (12.0)
Most or All of the Time (5-7 days)	17 (5.8)	24 (8.5)	41 (7.1)
I felt depressed.			
Rarely or None of the Time (Less than 1 day)	152 (52.2)	171 (60.4)	323 (56.3)
Some or a Little of the Time (1-2 days)	94 (32.3)	70 (24.7)	164 (28.6)
Occasionally or a Moderate Amount of the Time (3-4 days)	37 (12.7)	30 (10.6)	67 (11.7)
Most or All of the Time (5-7 days)	8 (2.7)	12 (4.2)	20 (3.5)
I felt that everything I did was an effort.			

Rarely or None of the Time (Less than 1 day)	140 (48.1)	117 (41.3)	257 (44.8)
Some or a Little of the Time (1-2 days)	77 (26.5)	87 (30.7)	164 (28.6)
Occasionally or a Moderate Amount of the Time (3-4 days)	38 (13.1)	43 (15.2)	81 (14.1)
Most or All of the Time (5-7 days)	36 (12.4)	36 (12.7)	72 (12.5)
I felt hopeful about the future.			
Rarely or None of the Time (Less than 1 day)	85 (29.2)	84 (29.7)	169 (29.4)
Some or a Little of the Time (1-2 days)	78 (26.8)	70 (24.7)	148 (25.8)
Occasionally or a Moderate Amount of the Time (3-4 days)	53 (18.2)	56 (19.8)	109 (19.0)
Most or All of the Time (5-7 days)	75 (25.8)	73 (25.8)	148 (25.8)
I felt fearful.			
Rarely or None of the Time (Less than 1 day)	175 (60.1)	159 (56.2)	334 (58.2)
Some or a Little of the Time (1-2 days)	82 (28.2)	79 (27.9)	161 (28.0)
Occasionally or a Moderate Amount of the Time (3-4 days)	25 (8.6)	32 (11.3)	57 (9.9)
Most or All of the Time (5-7 days)	9 (3.1)	13 (4.6)	22 (3.8)
My sleep was restless.			
Rarely or None of the Time (Less than 1 day)	142 (48.8)	135 (47.7)	277 (48.3)
Some or a Little of the Time (1-2 days)	95 (32.6)	89 (31.4)	184 (32.1)
Occasionally or a Moderate Amount of the Time (3-4 days)	31 (10.7)	33 (11.7)	64 (11.1)
Most or All of the Time (5-7 days)	23 (7.9)	26 (9.2)	49 (8.5)
I was happy.			
Rarely or None of the Time (Less than 1 day)	85 (29.2)	74 (26.1)	159 (27.7)
Some or a Little of the Time (1-2 days)	70 (24.1)	65 (23.0)	135 (23.5)
Occasionally or a Moderate Amount of the Time (3-4 days)	73 (25.1)	86 (30.4)	159 (27.7)
Most or All of the Time (5-7 days)	63 (21.6)	58 (20.5)	121 (21.1)
I felt lonely.			

Rarely or None of the Time (Less than 1 day)	158 (54.3)	161 (56.9)	319 (55.6)
Some or a Little of the Time (1-2 days)	89 (30.6)	83 (29.3)	172 (30.0)
Occasionally or a Moderate Amount of the Time (3-4 days)	23 (7.9)	26 (9.2)	49 (8.5)
Most or All of the Time (5-7 days)	21 (7.2)	13 (4.6)	34 (5.9)
I could not get “going”.			
Rarely or None of the Time (Less than 1 day)	168 (57.7)	174 (61.5)	342 (59.6)
Some or a Little of the Time (1-2 days)	78 (26.8)	69 (24.4)	147 (25.6)
Occasionally or a Moderate Amount of the Time (3-4 days)	35 (12.0)	29 (10.2)	64 (11.1)
Most or All of the Time (5-7 days)	10 (3.4)	11 (3.9)	21 (3.7)
Total CESD 10: mean (SD)	8.44 (4.38)	8.74 (4.8)	8.59 (4.59)

Table 4: Descriptive statistics for primary and secondary outcomes by study arm at baseline (where available), 3 month (where available) and 6 month. Frequencies and (percentages) are presented unless otherwise stated

TABLE 4: DESCRIPTIVE STATISTICS FOR PRIMARY AND SECONDARY OUTCOMES BY STUDY ARM AT BASELINE (WHERE AVAILABLE), 3 MONTH (WHERE AVAILABLE) AND 6 MONTH. FREQUENCIES AND (PERCENTAGES) ARE PRESENTED UNLESS OTHERWISE STATED.

	Baseline			Follow-up 3-month			Follow-up 6-month		
	Control	Intervention	Total	Control	Intervention	Total	Control	Intervention	Total
	Arm1	Arm2	Total	Arm1	Arm2	Total	Arm1	Arm2	Total
TB treatment status detailed									
Cured							108 (37.11)	105 (37.1)	213 (37.11)
Treatment completed							96 (33.0)	87 (30.74)	183 (31.88)
Treatment default							15 (5.2)	29 (10.25)	44 (7.67)
Treatment failure							5 (1.7)	2 (0.7)	7 (1.2)
Acquired drug resistance							1 (0.34)	4 (1.41)	5 (0.87)
Died							11 (3.78)	15 (5.30)	26 (4.53)
Transfer out							8 (2.75)	11 (3.89)	19 (3.31)
Unknown							42 (14.43)	25 (8.83)	67 (11.67)
Missing							5 (1.72)	5 (1.77)	10 (1.74)
TB treatment status binary (Primary outcome)**									
Not Successful							87 (29.9)	91 (32.16)	178 (31.01)
Successful							204 (70.10)	192 (67.84)	396 (68.99)
At least one positive smear result	85 (53.46)	96 (61.15)	181 (57.28)						
At least one positive Gene XPert result	184 (87.20)	178 (87.25)	362 (87.23)						
At least one positive culture result	11 (57.89)	10 (66.67)	21 (61.76)						

Sputum smear, Gene XPert, or culture result									
Negative	29 (12.45)	32 (14.16)	61 (13.29)						
Positive	204 (87.55)	194 (85.84)	398 (86.71)						
Conversion from positive to negative* **									
Yes							83(39.9)	85(43.59)	168(41.69)
No							125(60.1)	110(56.41)	235(58.31)
Continuous smoking abstinence among cigarette smokers at baseline									
Yes				27(16.27)	20(11.17)	47(13.62)	12(7.23)	10(5.59)	22(6.38)
No				139(83.73)	159(88.83)	298(86.38)	154(92.77)	169(94.41)	323(93.62)
Harmful or hazardous drinking[1]									
Had a drink in the past 12-months	208 (71.5)	223 (78.8)	431 (75.1)						
AUDIT score: mean (SD)	12.03 (4)	12.53 (3.93)	12.29 (3.96)						
Harmful or hazardous drinkers out of those who had a drink in the past 12-months at baseline (%)	188(90.38)	206(92.38)	394(91.42)	141	130	271	112	127	239
AUDIT Score (males): mean (SD) [max :19; min = 8]*!	13.14 (3.31)	13.61 (3.29)	13.39 (3.31)	8.20(6.08)	9.08(4.97)	8.63(5.58)	9.21(6.58)	8.24(5.41)	8.69(5.99)
AUDIT Score (females): mean (SD) [max :19; min = 7]*!	11.73 (3.52)	11.55 (3.6)	11.64 (3.54)	8.5(6.52)	8.15(6.44)	8.33(6.44)	7.67(6.84)	9.97(6.79)	8.89(6.86)
AUDIT score: mean (SD)	12.76 (3.42)	13.12 (3.47)	12.94 (3.45)	8.28(6.18)	8.84(5.38)	8.55(5.81)	8.79(6.66)	8.70(5.83)	8.74(6.22)
Difference from baseline				-4.61 (6.26)	-4.07(5.33)	-4.35(5.83)	-4.25(6.56)	-4.17(6.61)	-4.21(6.57)

Taking ART medication among HIV Positive patients	[163 (56.2)]	[142 (50.2)]	[305 (53.2)]	[122]	[83]	[205]	[100]	[83]	[183]
Yes	139 (85.28)	115 (80.99)	254 (83.28)	91 (74.6)	58 (69.9)	149 (72.7)	80 (80.0)	74 (89.2)	154 (84.2)
ART medication adherence									
Optimal adherence				101(99.02)	64(98.46)	165(98.8)	75(97.4)	64(96.97)	139(97.2)
Suboptimal adherence				1(0.98)	1(1.54)	2(1.2)	2(2.6)	2(3.03)	4(2.8)
TB medication adherence									
Optimal adherence				181(92.35)	138(90.79)	319(91.67)	61(89.71)	59(90.77)	120(90.23)
Suboptimal adherence				15(7.65)	14(9.21)	29(8.33)	7(10.29)	6(9.23)	13(9.77)

[1] hazardous/harmful drinkers who are not alcohol dependent= AUDIT score ≥ 8 for men or ≥ 7 for women but < 20

**Primary Outcome: in the published protocol paper "This is a binary variable defined as either successful treatment (cured or treatment completed) or failed treatment, death, acquired drug resistance, loss to follow-up or 'default', or not outcome evaluated.

*** Conversion from positive to negative: this was based on having a cured treatment outcome among those who were positive at baseline.

*! Important distinction at baseline for eligibility purposes.

TABLE 5: Number and type of adverse events at month 2, 3, and 6 by centre and study arm (see other document)

TABLE 5: Number and type of adverse events at month 2, 3, and 6 by centre and study arm							
Centre		Month 2		Month 3		Month 6	
	TYPE	Intervention	Control	Intervention	Control	Intervention	Control

TABLE 6: Regression analysis results for the primary and secondary outcomes at 6 months. Estimates presented with corresponding 95% CI. Crude and adjusted estimates are provided.

TABLE 6: Regression analysis results for the primary and secondary outcomes at 6 months. Estimates presented with corresponding 95% CI. Crude and adjusted estimates are provided.					
	Crude Odds Ratio (95% CI)*	P Value*	Adjusted Odds Ratio (95% CI)*	P Value*	
Primary outcome					
TB treatment status: Successful (**Ref: Not successful**)	0.9 (0.64,1.27)	0.548	0.86 (0.60,1.24)	0.421	
Secondary outcomes					
Sputum smear or culture result: converted from positive to negative (Ref: Not converted)	1.16 (0.83,1.63)	0.374	1.07‡ (0.76,1.51)	0.684	
Six-month continuous smoking abstinence among cigarette smokers at baseline (Ref: No)	0.76 (0.35,1.64)	0.482			
Taking ART medication among HIV positive patients!!	2.05 (0.80,5.27)	0.136			
TB medication adherence (Reference: Optimal)	0.89 (0.26,3.07)	0.849			
ART medication adherence (Reference: Optimal)	1.17 (0.14,9.94)	0.884			

	Study arm regression coefficient		Study arm regression coefficient		
AUDIT for those who were harmful or hazardous drinkers at baseline:**	-0.04 (-2,1.91)	0.966	0.02[!] (-1.55,1.6)	0.976	

* analyses accounted for potential clustering by centre.
† Number of participants whose outcome was treatment successful among the total number in the group.
‡ Adjusted for district, sex, and smoking/drinking status and HIV status at baseline
**Controlling for the AUDIT baseline values.
! Controlling for the AUDIT baseline values and adjusted for district, sex, and smoking/drinking status and HIV status at baseline
!! Adjusting for art status at baseline

TABLE 7: Regression analysis results for secondary outcomes measured at 3-months. Estimates presented with corresponding 95% CI. Crude and adjusted estimates are provided.

TABLE 7: Regression analysis results for secondary outcomes measured at 3-months. Estimates presented with corresponding 95% CI. Crude and adjusted estimates are provided.

	Crude Odds Ratio (95% CI)	P Value	Adjusted Odds Ratio (95% CI)	P Value	
Secondary outcome					
3-months continuous smoking abstinence among cigarette smokers at baseline	0.65 (0.37,1.14)	0.135			
Taking ART medication among HIV positive patients!!	0.79 (0.38,1.65)	0.53	0.74‡ (0.35,1.58)	0.443	
TB medication adherence (Reference: Optimal)	1.22 (0.52,2.87)	0.641			
ART medication adherence (Reference: Optimal)	1.58 (0.10,26.12)	0.750			
	Study arm regression coefficient		Adjusted estimates		
AUDIT for those who were harmful or hazardous drinkers at baseline**:	0.55 (-1.01,2.11)	0.474	0.74 (-0.62,2.1)	0.273	

* analyses accounted for clustering.
‡ Adjusted for district, sex, and smoking/drinking status and HIV status at baseline
**Controlling for the AUDIT baseline values.
! Controlling for the AUDIT baseline values and adjusted for district, sex, and smoking/drinking status and HIV status at baseline
!! Adjusting for art status at baseline

Additional tables
SMS-fidelity

Variable	**Intervention (N= ….) (=no. of participants allocated to intervention group, for example 245)**	**Control (N=…) (=no. participants allocated to control group, for example 248)**
No. of participants who received ALL due IMB messages INDEPENDENT OF WHETHER they completed MI 1 (i.o.w this is ITT analysis)	For example 120/245 (49 %)	For example 2/248 (…%)
Completion of first MI and initiation of SMS-sequence		
Completed first MI	n/N (%) (=No. who completed first MI in intervention arm/ no. participants allocated to intervention arm [%] For example 170/245 [69%])	n/N (%) (=No. who completed first MI in control/ no. participants allocated to control [%] For example 2/248)
No. of participants who received ALL due messages after receipt of MI1 and SMS sequence was generated (this is a type of Per Protocol analysis:	For example 120/170 (71%)	2/2

denominator limited to those who had MI1)				
SMS delivery for participants for whom the SMS-sequence was initiated (after receipt of first MI)				
	Mean (SD)	Median (IQR) Range	Mean (SD)	Median (IQR)
Average no. adherence messages received per participant (n=…) (n = the no. of participants who completed first MI, in this example 170)	For example 8 (3.4)	9 (7-10) Range 0-10	Expected to be 0 or close to it	Expected to be 0 or close to it
Average no. tobacco-related messages received (n=…) (n=no of participants who completed first MI AND were current tobacco users at baseline, for example 90)	For example 7 (3.4)	7 (6-7) Range 0-7	Expected to be 0 or close to it	Expected to be 0 or close to it
Average no. alcohol related messages received (n=…) (n=no. participants who completed first MI	For example 7 (3.4)	7 (6-7) Range 0-7	Expected to be 0 or close to it	Expected to be 0 or close to it

AND were drinkers at baseline=….for example 100)				
Average no. IMB messages received (n= total no who completed first MI)	For example 16 (4.5)	15 (10-20) Range 0-24	Expected to be 0 or close to it	Expected to be 0 or close to it

Other variables not yet analysed:

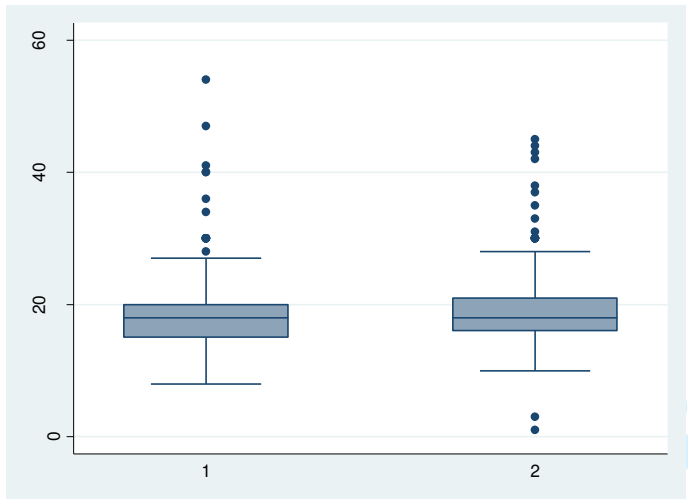
CESD at 3 and 6-month FU
Other smoking related questions at 3 and 6 month (quit intentions etc) but also SLT use at 3 and 6 month. (important because participants may have switched from tobacco smoking to SLT)
Other non-HE questions not yet analysed

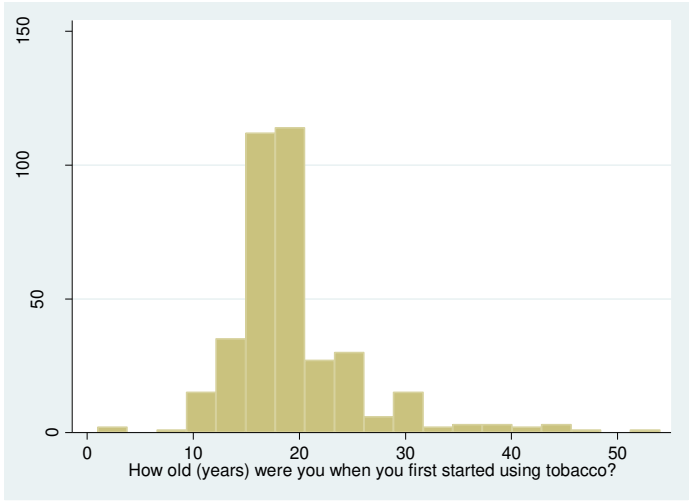
13. Additional descriptive Statistics

TABLE 8: Additional Descriptive statistics for characteristics at baseline by study arm. Frequencies and (percentages) are presented unless otherwise stated

		Baseline		
	N1/N2	Intervention	Control	Total
		Arm 1	Arm 2	
TYPE OF MINE WORK	46/45			91
Coal		7 (15.2)	3 (6.7)	10 (11.0)
Diamond		3 (6.5)	1 (2.2)	4 (4.4)
Gold		13 (28.3)	17 (37.8)	30 (33.0)
Platinum and palladium		24 (52.2)	17 (37.8)	41 (45.1)
Chromium		11 (23.9)	12 (26.7)	23 (25.3)
Uranium		1 (2.2)	1 (2.2)	2 (2.2)
Manganese		0(0)	0(0)	0(0)
Other		0(0)	0(0)	0(0)
Total Types of Mines worked in				
1	73			
2	12			
3	3			
4	1			

Exact Distribution for number smoked in the past seven days				
0		24 (14.5)	16 (8.9)	40 (11.6)
1		4 (2.4)	4 (2.2)	8 (2.3)
2		4 (2.4)	3 (1.7)	7 (2.0)
3		5 (3.0)	13 (7.3)	18 (5.2)
4		13 (7.8)	8 (4.5)	21 (6.1)
5		5 (3.0)	17 (9.5)	22 (6.4)
6		1 (0.6)	3 (1.7)	4 (1.2)
7		110 (66.3)	115 (64.2)	225 (65.2)
new_a_positive_TB				
0		29 (11.98)	33 (14.35)	62 (13.14)
1		122 (50.41)	104 (45.22)	226 (47.88)
2		80 (33.06)	81 (35.22)	161 (34.11)
3		11 (4.55)	12 (5.22)	23 (4.87)





Age started smoking

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-5
	2b	Specific objectives or hypotheses	5-7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5-6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7-8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	6

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10, Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	10, Fig 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5-6
	14b	Why the trial ended or was stopped	10,21
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1 and 2, Supp Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Fig 1, Table 3
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Table 3,4,5
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Only relative effect
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Table 4, 5
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	No harms reported
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	21-22
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	NA, no effect
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	21
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	Published paper referenced

Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	23

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Effect of a brief motivational interview and text message intervention targeting tobacco smoking, alcohol use, and medication adherence to improve tuberculosis treatment outcomes in adult patients with tuberculosis: a multicentre, randomised controlled trial of the ProLife programme in South Africa

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ABSTRACT

Objectives: to investigate the effectiveness of a complex behavioural intervention, ProLife, on tuberculosis (TB) treatment success, medication adherence, alcohol use and tobacco smoking.

Design: multi-centre, individual, randomised controlled trial where participants were assigned (1:1) to the ProLife intervention or usual care.

Setting: 27 primary care clinics in South Africa.

Participants: 574 adults starting treatment for drug-sensitive pulmonary TB who smoked tobacco or reported harmful/hazardous alcohol use.

Interventions: The intervention, delivered by lay health workers (LHWs), consisted of 3 brief motivational interviewing (MI) sessions, augmented with Short Message Service (SMS) messages, targeting medication adherence, alcohol use and tobacco smoking.

Outcome measures: the primary outcome was successful versus unsuccessful TB treatment at 6 to 9 months, from TB records; secondary outcomes: biochemically confirmed sustained smoking cessation, reduction in the Alcohol Use Disorder Identification Test (AUDIT) score, improved TB and antiretroviral treatment (ART) adherence and ART initiation, each measured at 3 and 6 months by questionnaires; cure rates in patients who had bacteriology-confirmed TB at baseline, from TB records.

Results: Between 15 November 2018 and 31 August 2019, 574 participants were randomised to receive either the intervention (n=283) or usual care (n=291). TB treatment success rates did not differ significantly between intervention (67.8%) and control (70.1%) (OR=0.9 (95% CI: 0.64,1.27)). There was no evidence of an effect at 3- and 6-months respectively on continuous smoking abstinence (OR=0.65 (95% CI: 0.37,1.14); OR=0.76 (95% CI: 0.35,1.63)), TB medication adherence (OR=1.22 (95%CI: 0.52,2.87); OR=0.89 (95%CI: 0.26,3.07)), taking ART (OR=0.79 (0.38,1.65), OR=2.05 (0.80,5.27)) or AUDIT scores (mean score difference 0.55 (95% CI: -1.01,2.11); -0.04 (95% CI: -2,1.91); and adjusting for baseline values. Cure rates were not significantly higher (OR=1.16 (0.83,1.63)).

Conclusions: Simultaneous targeting of multiple health risk behaviours with MI and SMS using LHWs may not be an effective approach to improve TB outcomes.

Trial registration: ISRCTN62728852, Registered on 13th April 2018.

Key words: Tuberculosis, smoking, alcohol, motivational interviewing, mHealth, anti-retroviral therapy, adherence

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The use of motivational interviewing combined with Short Text Messaging to address the effect of multiple risk behaviours (smoking, drinking and poor adherence) on tuberculosis ~~TB~~ treatment outcomes is a novel and much needed intervention.
- Our study design was strong: this was a multi-site individually randomised controlled trial with a large sample size and a high follow up rate for the primary outcome.
- We used validated measurement tools; furthermore data analysis and primary outcome assessment were blinded, thereby limiting measurement bias.
- The study was underpowered for secondary outcomes. ~~T~~Low~~he~~ intervention uptake may have diluted any potential intervention effects.

INTRODUCTION

Tuberculosis (TB) is among the most common chronic infectious diseases in the world today. In 2019, 1.4 million deaths worldwide were attributed to TB, and the majority of these occurred in low-income and middle-income countries (LMICs).(1) South Africa not only has one of the highest TB burdens in the world; it is faced with high TB treatment interruption and loss to follow-up rates. ~~of the 30 high TB burden countries.~~ It also has a high prevalence of human immunodeficiency virus (HIV) co-infection in patients with TB and a relatively high mortality in these co-infected patients.(1) Studies of interventions to advance the goal of ending the TB epidemic and improving treatment outcomes are therefore research priorities in South Africa and other LMICs.(2)

Mortality and morbidity from TB is strongly associated with health risk behaviours, particularly smoking and hazardous or harmful alcohol use, both of which are prevalent and often co-occur in ~~TB~~ patients with TB.(3–10) Strategies are also required to improve TB medication adherence in patients with TB and adherence to TB medication and anti-retroviral therapy (ART) in ~~TB-HIV co-infected~~ patients co-infected with TB and HIV, both of which may be negatively influenced by excessive alcohol use.(1) There is very limited research on how to concurrently tackle these three risk behaviours - namely smoking, harmful alcohol use and poor medication adherence - in patients with TB, particularly in LMICs.

Motivational Interviewing (MI) ~~is a counselling technique known to facilitate behaviour change,(11) and~~ has been shown to~~effectively~~ support reduced drinking, smoking cessation in TB patients and TB treatment and/or antiretroviral therapy (ART) medication adherence.(11–13) MI interventions can be effectively delivered by lay health workers (LHWs).(14) The more widespread use of LHWs and the increased use of mobile health (mHealth) digital technologies represent promising ways to increase the scalability of MI interventions. Indeed, the World Health Organisation (WHO) has called for researchers to capitalise on advances in mobile phone technology, network coverage and the increased use of common and widely available digital technologies (including the mobile phone short message service (SMS)) to improve TB care.(15) There is ~~robust~~ evidence that mHealth technologies can have modest beneficial effects on a range of health outcomes, including medication adherence.~~(16)~~(16,17) Mobile phone messaging also shows a modest effect in improving TB treatment success rates.(18,19) The evidence is however stronger for two-way messaging and interactive systems for which smart phones are required.(18) These are often not available to patients with TB in Africa.(20) ~~An SMS intervention in co-infected TB/HIV patients demonstrated effectiveness in increasing adherence to ART,(17) although the existing evidence is not of sufficient quality to know if this consistently applies to medication adherence in TB patients.(18)~~

A limitation of existing MI and mHealth interventions is that they have been studied in the context of modifying a single lifestyle factor. Integrated interventions are likely to be better accepted and more effective than multiple interventions targeting different health risk factors.(21,22) In the case of TB, there is a need for an intervention that has the flexibility to target multiple lifestyle factors as appropriate and in line with patient preferences. This could be achieved through increased integration of TB and non-communicable disease services.(23)

Recent re-engineering of primary health care in South Africa has seen the introduction of municipal ward-based primary healthcare outreach teams of community health workers (CHWS). CHWs work in an integrated, team-based manner, supported by nurses, and take responsibility for health education and promotion, counselling and support for a range of health conditions.(24,25) Task shifting in this context has been shown to improve population health in LMICs (26) and these teams can be trained and supported to take responsibility for TB/HIV care.(27) Integrated interventions could be implemented within this framework in a feasible and scalable way to improve outcomes for patients with TB across South Africa and beyond.

Building on previous successes with MI and mHealth interventions, we developed a complex behavioural intervention (ProLife) comprising MI-based counselling and SMS, targeting three lifestyle risk behaviours for poor TB outcomes (smoking, hazardous/harmful alcohol consumption and poor medication adherence), and delivered by LHWs. We then conducted a randomised controlled trial (RCT) to assess the effectiveness of the ProLife intervention on improving TB treatment outcomes, smoking abstinence, reducing alcohol consumption and improving adherence to TB and ART medication compared to usual care. The cost-effectiveness of the intervention was also assessed but only the costing results will be presented in this paper.

METHODS

Study design and participants

This was a prospective, two-arm, multi-centre, individually ~~randomised controlled trial~~RCT, which took place across 27 primary care clinics in 3 districts in South Africa (Lejweleputswa in the Free State province; Bojanala in the North West province; and Sedibeng in Gauteng province). Adult patients (18 years or older) were eligible for the study if they had drug-sensitive Pulmonary TB (PTB), and were initiating TB treatment or had been on TB treatment for less than a month for this

treatment episode (both "new" and "retreatment patients"). They had to be tobacco smokers (defined as smoking daily or non-daily in the last four weeks on the Global Adult Tobacco Survey questionnaire)(28) and/or hazardous/harmful drinkers who were not alcohol dependent (Alcohol Use Disorders Identification Test (AUDIT) score ≥ 8 for men or ≥ 7 for women but <20).(29) They also had to have access to a mobile phone and understand one of the 4 languages used for the trial (English, IisiZulu, SeSotho and Setswana). Potential participants were recruited consecutively at the participating clinics between 15 November 2018 and 31 August 2019. Trained field workers identified those interested in the study and screened them for eligibility. If eligible and willing to be enrolled into the trial, written informed consent was obtained. The RCT received ethics approval from the Research Ethics Committees of the five participating research institutions.(30)

Randomisation and blinding

Patients were centrally randomised (1:1) to the ProLife intervention or control group using a randomised sequence generator by the trial statistician (MK) who was blind to the arm allocation. We used block randomisation with varying block sizes stratified by clinic so as to achieve equal numbers in intervention and control groups within each clinic. Fieldworkers used sequentially numbered, sealed, opaque envelopes to allocate participants to intervention or control. ProLife involved a complex behavioural intervention therefore LHWs and participants could not be blinded to the intervention. However, the determination of the primary outcome was done by the TB nurses who were blinded to the intervention status of the participants, based on routinely collected data. The statistician (MK) was blinded to the intervention or control arm allocation of participants during the analysis.

Intervention and procedures

The ProLife intervention was developed based on a conceptual framework, following a review of pre-existing evidence.(31) This framework assumed that smoking cessation, reducing harmful alcohol use and improved adherence to TB and HIV treatment would result in improved TB treatment outcomes.(30) The intervention consisted of 3 brief MI counselling sessions, lasting 15-20 minutes, one month apart, delivered by trained LHWs at their TB clinic. The first MI session took place immediately or shortly after the randomisation and involved prioritisation and agenda setting, wherein the participant determined which factor should be prioritised (either a plan to quit tobacco smoking, or reduce or quit drinking, or deal with barriers relating to ART or TB medication adherence). The second and third sessions built on the previous one until all relevant behavioural problems had been addressed. These sessions were reinforced with follow-up SMS text messages, twice a week over 12 weeks.(30) Study patients received 10 TB-related messages followed by seven alcohol reduction- and/or seven smoking cessation-related messages, as appropriate. Messages were aimed at giving information, and augmenting motivation or behavioural skills (we refer to the feasibility paper for more details).(31) Applicable SMS-messages were automatically activated after

the first MI had taken place. Thereafter the remaining messages were delivered even if the participant did not attend the second or third MI session.

Participants randomised to the ProLife intervention also received the same "usual care" as those in the control group. The control group received the usual care and routine treatment and support offered to ~~TB~~ patients with TB in South Africa, which varies by district but includes: health education; dietetic input; social support; point of care biochemical testing; and HIV testing with pre- and post-test HIV test counselling.

Data were collected at baseline, 3- and 6-months and recorded by fieldworkers equipped with mobile phones with the ProLife mobile data collection application (built with CommCare)(32) installed. They used a standardised electronic case report form (CRF) and followed standard operating procedures (SOPs) to ensure quality. Details of data collection, protection and storage procedures have been reported elsewhere.(30)

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Outcomes

Primary Outcome

The primary outcome of TB treatment success at 6 to 9 months follow-up (depending on when it was recorded) was as per the WHO definitions adopted in South Africa,(10) that is, either successful treatment (cured or treatment completed) or failed treatment, death, acquired drug resistance, loss to follow-up (defined as treatment interruption of more than 2 months), or outcome not evaluated. It was measured using the routinely collected TB treatment outcomes in patients' individual files.

Secondary Outcomes

For those participants with bacteriologically confirmed PTB at baseline (either sputum acid fast bacilli (AFB) positive, culture positive or GeneXpert positive PTB), sputum conversion at the end of treatment ("cure rate") was measured as a secondary outcome.(10) Continuous smoking abstinence was assessed at 3- and 6-months follow-up in those participants who were current cigarette smokers at baseline. It was defined as having quit smoking completely and a self-report of not smoking more

than 5 cigarettes from the start of the study, in addition to a negative biochemical test (exhaled Carbon Monoxide (CO) < 7 ppm).(33,34) Changes in alcohol consumption were computed using the AUDIT questionnaire scores measured at 3- and 6-months follow-up in those participants who were hazardous/harmful drinkers at baseline.

HIV positive participants were asked about ART status at baseline, 3- and 6-months using standardised questions on the CRF and change in ART status as measured at the 2 follow-up times.

TB and ART medication adherence was measured using modified versions of the AIDS Clinical Trials Group Adherence Questionnaire, a validated tool for measuring adherence specifically to ART.(35) Adherence was measured using an adherence index calculated by the formula (using the 4-day recall): [Total number of doses taken/Total number of doses prescribed] x 100. Patients with at least 95% adherence were classed as having optimal adherence and those with less than 95% were classed as having low (or suboptimal) adherence. This was assessed at 3- and 6-months.

During COVID-19 lockdown (in the second term of 2020) we switched to telephonic follow-up of participants using a shortened questionnaire whereby only strictly needed information for the measurement of outcomes was inquired about.

Training and Intervention Fidelity Monitoring

The training and intervention fidelity monitoring is described in more detail in previous papers.(30,31) In brief, 18 LHWs, 3 district coordinators and 1 research assistant who focused on counselling supervision underwent MI training over 5 days. LHWs completed a post-session semi-structured form onto which they indicated the extent to which they implemented each element of MI, as well as their general qualitative impressions of that particular session. In addition, we assessed MI intervention fidelity based on ratings of the counsellors' recorded MI sessions, as described below and in footnotes to the relevant~~Supplementary~~ table ~~4~~. SMS-message delivery was also assessed.

Economic evaluation

The ProLife intervention costs consisted of the costs of training and the delivery of the ProLife intervention, including relevant personnel involvement (trainers and LHWs), materials used, travel, accommodation and refreshments, and digital infrastructure for the intervention. These were estimated based on research team records. Usual care costs consisted of TB medication costs, biochemical investigations, and ART costs if applicable. These were estimated based on information obtained through routine records. The country specific version of Euroqol with 5 dimensions and

with 3 levels of response categories (EQ-5D-3L) for South Africa was administered to participants at baseline, 3- and 6-months follow-up to measure health-related quality of life.(36,37)

Statistical analysis

The sample size was estimated at 696 in total (348 participants per arm), to detect a 10% difference in TB treatment success rates (0.86 vs. 0.76) in the ProLife arm (intervention) vs. the control arm with 80% power, a significance level of 0.05 and 25% attrition rate. The assumed success rates in the control group were based on actual success rates in TB patients with TB in the studied provinces obtained from TB managers at the time of the grant application for this study.

We summarised baseline data descriptively by trial arm. For the primary outcome, we conducted statistical analysis on an intention-to-treat basis. We used binary logistic regression to compare the main outcome (TB treatment success rate) between the intervention and the usual care arm. Where treatment outcome data were missing, the outcome was coded as unsuccessful. TB treatment outcomes recorded by the TB nurse were taken on face value as inconsistencies in the dates of bacteriological results did not permit us to verify the correctness of the nurse assessment. We carried out similar statistical analyses for the secondary outcomes with appropriate regression techniques. For the reduction in harmful or hazardous drinking, we used linear regression to estimate the difference in total AUDIT score between control and intervention groups accounting for the baseline AUDIT score as covariate. Separate analyses at 3- and 6-months were performed.

For our main analyses we adjusted for baseline characteristics if these differed between trial arms at baseline. The covariates that we controlled for in each model are specified when a model is presented. The statistical packages STATA (38) and R (39) were used to carry out the analyses, with a P-value < 0.05 considered statistically significant.

The validated Motivational Interviewing Treatment Integrity (MITI) coding tool (version 4.2.1) was used to assess MI intervention fidelity.(40) The coding entailed making 'Global Ratings' (on 4 dimensions: Cultivating change talk, Softening sustain talk, Partnership and Empathy) and 'Behaviour' counts (with respect to the items: giving information, persuade, persuade with permission, question, simple reflection, complex reflection, affirm, seeking collaboration, emphasising autonomy and confront). A score was assigned to each of these items and the scores compared against the competency and proficiency thresholds that are specified in the MITI manual.

For the analysis of the costs, all costs were collected in South Africa Rand (ZAR) except for the data management system subscription. Results are presented in both ZAR and US dollar ($) using the 2019 OECD exchange rate (1 USD = 14.448 Rand).(36) No South African specific valuation set was available for EQ-5D-3L. The valuation set of Argentina, based on a Visual Analogue Scale ~~for EQ-5D-3L~~, was used to derive utility values, because the GDP per capita in international dollars was the closest between the two countries at the time of analysis.(37,41) Quality-adjusted life years (QALYs) were derived from the utility values at the time points by calculating the area under the curve.(42) No missing data imputation was performed.

RESULTS

Participant enrolment and follow-up

A total of 2099 ~~TB~~ patients with TB were screened for eligibility out of which 574 consenting and eligible participants were randomised: 291 to control and 283 to intervention. Trial recruitment was terminated on 31 August 2019 before the planned sample size was reached because of budget and time constraints. In the intervention arm, 227 (80.2%) participants completed the first MI (MI 1) session, 199 (70.3%) MI 2 and 150 (53.0%) MI 3. In the intervention arm, at least one message was delivered to 208 (73.5%) participants, while 99 (35.0%) received all messages. Of those randomised to the control and intervention groups, the primary outcome was recorded in 244 (83.8%) and 253 (89.4%) participants, respectively. (Figure 1)

Figure 1 Consort flow diagram

Baseline participant characteristics of the intervention and control arm

Socio-demographic; socio-economic and clinical characteristics

Baseline characteristics were distributed similarly in the intervention and control arms for most variables but with some imbalances in educational level. A total of 513 (91.3%) participants were new ~~TB~~ patients with TB, 129 (22.5%) women, and nearly all had PTB (International Classification of Diseases-10 A15) without extrapulmonary TB manifestations (553 (98.9%)). About half of the participants were HIV positive (305 (53.2%)), of whom 204 (65.4%) were on cotrimoxazole and 257 (82.4%) were on ART. (Table 1) Details of marital status, employment, wealth, depression status and co-morbidities are presented in Supplementary table 1.

Table 1 Baseline descriptive socio-economic statistics and clinical characteristics by study arm

	Control (N = 291) n (%)*	Intervention (N = 283) n (%)*	Total (N=574) n (%)*
Age in years: mean (SD)	39.37 (12.60)	38.56 (11.15)	
Female Sex	69 (23.7)	60 (21.2)	129 (22.5)
Education			
No education	7 (2.4)	5 (1.8)	12 (2.1)
Grades 1-5	23 (7.9)	20 (7.1)	43 (7.5)
Grades 6-7	32 (11.0)	35 (12.4)	67 (11.7)
Grades 8-11	96 (33.0)	128 (45.2)	224 (39.0)
Grade 12	87 (29.9)	70 (24.7)	157 (27.4)
Higher	24 (8.2)	8 (2.8)	32 (5.6)
Declined to answer**	22 (7.6)	17 (6.0)	39 (6.8)
TB Patient category			
New patient	264 (92.3)	249 (90.2)	513 (91.3)
Relapse	10 (3.5)	9 (3.3)	19 (3.4)
Re-treatment after default	9 (3.1)	14 (5.1)	23 (4.1)
Re-treatment after failure	1 (0.3)	2 (0.7)	3 (0.5)
Other	2 (0.7)	2 (0.7)	4 (0.7)
TB Site of disease Pulmonary only (ICD-10 A15)	281 (98.9)	272 (98.9)	553 (98.9)
TB Sputum smear, Gene XPert, or culture result available N=	236	227	463
At least one Sputum smear, Gene XPert, or culture result positive	208 (88.1)	195 (85.9)	403 (87.0)
HIV status			
Negative	118 (40.7)	125 (44.2)	243 (42.4)
Positive	163 (56.2)	142 (50.2)	305 (53.2)
Unknown	9 (3.1)	16 (5.7)	25 (4.4)
HIV positive patients			
Using Cotrimoxazole	104 (63.8)	100 (67.1)	204 (65.4)
Using anti-retroviral	139 (85.3)	118 (79.2)	257 (82.4)

* Frequencies and (percentages) are presented unless otherwise stated
**More variables with the option "declined to answer" are listed in the Supplementary table 1

Table 2 Baseline descriptive alcohol and smoking characteristics by study arm

	Control (N=291) n (%)*	Intervention (N=283) n (%)*	Total (N=574) n (%)*
In the past month, smoked tobacco			
Not at all**	110 (37.8)	92 (32.5)	202 (35.2)
Daily	149 (51.2)	149 (52.7)	298 (51.9)
Less than Daily	32 (11.0)	42 (14.8)	74 (12.9)
Had a drink in the past 12-months	208 (71.5)	223 (78.8)	431 (75.1)
AUDIT Score (males) : mean (SD) [max: 19]†	12.27 (3.98)	13.02 (3.78)	12.66 (3.89)
AUDIT Score (females): mean (SD) [max: 19]†	11.32 (4.02)	10.98 (4.02)	11.15 (4.0)
Hazardous/harmful drinking and Smoking Combined (Constructed)			
Hazardous/harmful drinking Only‡	110 (37.8)	92 (32.5)	202 (35.2)
Smoking Only	103 (35.4)	77 (27.2)	180 (31.4)
Smoking and hazardous/harmful drinking‡	78 (26.8)	114 (40.3)	192 (33.4)

* Frequencies and (percentages) are presented unless otherwise stated
**Non-smokers were only included if they were harmful or hazardous drinkers
†Only hazardous/harmful drinkers and/or current smokers were included in the study. Therefore ~~TB~~ patients with TB were excluded if they were non-current smokers and had an AUDIT score <7 (females) or <8 (males) or >19; however, they were included if they were smokers independent of whether they had a drink in the past year and therefore independent of the AUDIT score. These AUDIT scores are thus representative of the mean AUDIT scores in the entire study sample and differ from the AUDIT score in the harmful/hazardous drinkers whose change in AUDIT score was measured at 3 and 6-months follow-up ~~(see Table 3)~~
‡Harmful/hazardous drinking is defined as Alcohol Use Disorders Identification Test (AUDIT) score ≥ 8 for men or ≥ 7 for women but <20

There were 372 current smokers (298 daily, 74 less than daily). Seventy eight participants (26.8 %) in the control arm were dual smokers *and* drinkers compared to 114 (40.3 %) in the intervention arm. In the control arm, 110 (37.8%) were hazardous/harmful drinkers only and 103 (35.4%) were smokers only, compared to 92 (32.5%) and 77 (27.2) respectively, in the intervention arm. (Table 2) More details of smoking and drinking history, forms of tobacco use, addiction and quit attempts are presented in Supplementary Table 2.

Primary outcome

Overall, 396 (70%) of participants were classified as treated successfully (treatment completed or cured). The remainder either interrupted treatment, failed treatment, developed drug resistance, wereas transferred out or had an unknown ~~the~~ treatment outcome.(Supplementary table 3) The percentage of successful TB treatment did not differ significantly between the control and intervention arm (70.1% vs. 67.8%), odds ratio (OR) for successful TB treatment 0.90 (95%CI: (0.64,1.27)) comparing the intervention arm to the control arm; and was similar to adjusted ORs. (Tables 3 and 4)

Secondary outcomes

Cure rates

Among the 403 participants who had at least one positive bacteriological result at baseline, 168 (41.7%) were recorded as cured; of these, 83/205 (39.9%) were in the control arm compared to 85/195 (43.6%) in the intervention arm. The OR of being cured was 1.16 (95% CI: 0.83,1.63) in the intervention versus the control arm; and was similar to the adjusted OR. (Tables 3 and 4)

Continuous smoking abstinence

Among those who identified as cigarette smokers at baseline (345 (60.1%)), 27 had information (self-report plus biochemical verification) to enable the identification of continuous abstinence at 6-months of which 22 had continuously abstained from smoking. These were similarly distributed across the two study arms: 10 (5.59%) participants in the intervention arm compared to 12 (7.23%) in the control arm, OR 0.76 (95% CI: 0.35,1.63). (Tables 3 and 4) At the 3-month follow-up 20 (11.2%) participants in the intervention arm compared to 27 (16.3%) in the control arm continuously abstained from smoking, OR 0.65 (95% CI: 0.37,1.14). (Tables 3 and 5)

TABLE 3 Descriptive statistics for primary and secondary outcomes by study arm at baseline (where available), 3-months (where available) and 6-months

	Baseline n (%)*			3-months follow-up n (%)*			6-months follow-up n (%)*		
	Control	**Intervention**	**Total**	**Control**	**Intervention**	**Total**	**Control**	**Intervention**	**Total**
TB treatment status[a]									
Successful**							204 (70.1)	192 (67.8)	396 (69.0)
Not Successful							87 (29.9)	91 (32.16)	178 (31.01)
Cured [a, ***									
Yes							83 (39.9)	85 (43.6)	168 (41.7)
No							125 (60.1)	110 (56.4)	235 (58.3)
Continuous smoking abstinence[b]									
Yes				27 (16.3)	20 (11.2)	47 (13.6)	12 (7.2)	10 (5.6)	22 (6.4)
No				139 (83.7)	159 (88.8)	298 (86.4)	154 (92.8)	169 (94.4)	323 (93.6)
Harmful/hazardous drinkers[l]: N =	188†	206†	394†	141†	130†	271†	112†	127†	239†
AUDIT score: mean (SD)	12.76 (3.42)	13.12 (3.47)	12.94 (3.45)	8.28 (6.18)	8.84 (5.38)	8.55 (5.81)	8.79 (6.66)	8.70 (5.83)	8.74 (6.22)
Difference from baseline: mean (SD)				-4.61 (6.26)	-4.07 (5.33)	-4.35 (5.83)	-4.25 (6.56)	-4.17 (6.61)	-4.21 (6.57)
HIV positive patients:	163† (56.2)	142† (50.2)	305† (53.2)	122†	83†	205†	100†	83†	183†
Taking ART medication if HIV positive‡	139 (85.3)	115 (81.0)	254 (83.3)	91 (74.6)	58 (69.9)	149 (72.7)	80 (80.0)	74 (89.2)	154 (84.2)

ART medication adherence[b]						
Optimal adherence	101 (99.0)	64 (98.5)	165 (98.8)	75 (97.4)	64 (97.0)	139 (97.2)
Suboptimal adherence	1 (1.0)	1 (1.54)	2 (1.2)	2 (2.6)	2 (3.0)	4 (2.8)
TB medication adherence						
Optimal adherence	181 (92.3)	138 (90.8)	319 (91.7)	61 (89.7)	59 (90.8)	120 (90.2)
Suboptimal adherence	15 (7.6)	14 (9.2)	29 (8.3)	7 (10.3)	6 (9.2)	13 (9.8)

a: only assessed at 6-months

b: assessed at 3 and 6-months; this table refers to *cigarette* smokers only (other forms of tobacco smoking are excluded)

* Frequencies and (percentages) are presented unless otherwise stated

**Primary Outcome: This is a binary variable defined as either successful treatment (cured or treatment completed) or failed treatment, death, acquired drug resistance, loss to follow-up or treatment interrupted for more than 2 months, or outcome not evaluated/unknown.

***Based on having a cured treatment outcome among those who were bacteriologically positive at baseline.

! hazardous/harmful drinkers who are not alcohol dependent= AUDIT score ≥ 8 for men or ≥ 7 for women but < 20; *! Important distinction at baseline for eligibility purposes.

†Denominator for the mean (SD) or denominator for %

‡ Information on HIV-positivity was obtained from information from TB records combined with patient self-report at baseline. True HIV-positivity rates may have been higher.

TABLE 4 Regression analysis results for the primary and secondary outcomes at 6-months

	Crude Odds Ratio (95% CI)*	P Value*	Adjusted Odds Ratio (95% CI)*	P Value*
Primary outcome				
TB treatment status: Successful (Ref: Not successful)	0.90 (0.64,1.27)	0.548	0.86‡ (0.60,1.24)	0.421
Secondary outcomes				
Cured (Ref: Not Cured)	1.16 (0.83,1.63)	0.374	1.07‡ (0.76,1.51)	0.684
Continuous smoking abstinence (Ref: No)***	0.76 (0.35,1.63)	0.482		
TB medication adherence (Ref: Optimal)	0.89 (0.26,3.07)	0.849		
ART medication adherence (Ref: Optimal)	1.17 (0.14,9.94)	0.884		
Taking ART medication (Ref: No)	2.05! (0.80,5.27)	0.136		
AUDIT	-0.04** (-2,1.91)	0.966	0.02!! (-1.55,1.6)	0.976

* Analyses accounted for potential clustering by centre.
‡ Adjusted for district, sex, and smoking/drinking status and HIV status at baseline. It is worth noting that of the variables in the adjusted model; the only statistically significant result is for the district variable.
! Adjusting for art status at baseline
**Controlling for the AUDIT baseline values. The values represent the study arm regression coefficient.
!! Controlling for the AUDIT baseline values and adjusted for district, sex, and smoking/drinking status and HIV status at baseline. The values represent the study arm regression coefficient.
***Given the limited number of those who were identified as continually abstained, we were only able to adjust for one additional variable at a time. Adding one of the following variables: heaviness of smoking, type of drinker at baseline, age when started smoking, and the duration of smoking at baseline; the adjusted odds ratio of continuous abstinence comparing the intervention to the control arm ranged between 0.73 and 0.76 with similar confidence limits as for the crude estimate

TABLE 5 Regression analysis results for secondary outcomes measured at 3-months

Secondary outcome	Crude Odds Ratio (95% CI)*	P Value*	Adjusted Odds Ratio (95% CI)*	P Value*
Continuous smoking abstinence (Ref: No)**	0.65 (0.37,1.14)	0.135		
TB medication adherence (Ref: Optimal)	1.22 (0.52,2.87)	0.641		
ART medication adherence (Ref: Optimal)	1.58 (0.10,26.12)	0.750		
Taking ART medication (Ref: No)	0.79! (0.38,1.65)	0.53	0.74‡ (0.35,1.58)	0.443
AUDIT	0.55† (-1.01,2.11)	0.474	0.74!! (-0.62,2.1)	0.273

*Analyses accounted for clustering.
! Adjusting for art status at baseline
‡ Adjusted for art status at baseline, district, sex, and smoking/drinking status and HIV status at baseline.
†Controlling for the AUDIT baseline values. The values represent the study arm regression coefficient.
!! Controlling for the AUDIT baseline values and adjusted for district, sex, and smoking/drinking status and HIV status at baseline. The values represent the study arm regression coefficient.
** Given the limited number of those who were identified as continually abstained, we were only able to adjust for one additional variable at a time. Adding one of the following variables: heaviness of smoking, type of drinker at baseline, age when started smoking, and the duration of smoking at baseline; the adjusted odds ratio of continuous abstinence comparing the intervention to the control arm ranged between 0.63 and 0.66 with similar confidence limits as for the crude estimate.

Change in harmful/hazardous drinking

AUDIT scores were about 4 points lower at both follow-up times than at baseline, independent of the intervention.(Table 3) In the intervention arm, participants had, on average, a reduction of 0.04 points (95% CI: -2,1.91) on the AUDIT score at 6-months, compared to those in the control arm controlling for baseline scores; whereas an average increase of 0.55 (95% CI: -1.01,2.11) was observed at 3-months. (Tables 4 and 5)

Medication adherence and ART uptake

At 6-months, the OR of taking ART medication was 2.05 (95% CI: 0.80,5.27) comparing the intervention arm to the control arm and controlling for ART baseline medication status; whereas it was 0.79 (95% CI: 0.38,1.65) at 3-months. The proportion of participants who had optimal TB medication adherence was 90.2% (120/133) at 6-months and 91.7% (319/348) at 3-months. Suboptimal TB medication adherence ORs were 0.89 (95%CI: 0.26,3.07) and 1.22 (95%CI: 0.52,2.87) comparing intervention arm to the control arm at 6-months and 3-months, respectively. The proportions of participants on ART who had optimal ART medication adherence were high at both 3-months (165/167, 98.8%) and 6-months follow-up (139/143, 97.2%). Suboptimal ART medication adherence ORs were 1.17 (95%CI: 0.14,9.94) and 1.58 (95%CI: 0.10,26.12) comparing the intervention arm to the control arm at 6-months and 3-months, respectively. (Tables 3, 4 and 5)

Intervention fidelity

Motivational interviewing fidelity

The recordings of 17 counsellors (one each) were transcribed verbatim and then assessed. In terms of the global ratings, the LHWs' counselling sessions were above proficiency levels on all items, namely, cultivating change talk, softening sustain talk, partnership, and empathy (as the mean scores were all above 2). In terms of the summary measures, the LHWs' counselling sessions did not achieve the basic proficiency threshold of 3.5 for the Relational component (Partnership + Empathy) as their mean score was 3.1 (SD=1.19). However, their mean score on the Technical component (Cultivating Change Talk + Softening Sustain Talk) of 3.3 (SD=0.97) was above the threshold of 3. For behavioural counts, "Asking Questions" had the highest mean score (24.2; SD=10.42), followed by "Affirm" with a mean score of 5.5 (SD=3.7). The counsellors were least likely to engage in the following: Persuade with permission and emphasising autonomy. The mean Reflections to Questions Ratio was 0.23 (SD=0.24). The LHWs made on average 9.3 (SD=4.74) MI adherent (Affirm, Emphasize Autonomy and Seek Collaboration) and 1.2 (SD=2.28) MI non-adherent (Confront and Persuade) statements per session. (Supplementary Ttable 4)

SMS-delivery

Of the total number of Information-Motivation-Behaviour messages triggered, 3583 (80.4%) were delivered. All due SMS messages were delivered to 95 (41.9%) of the participants who completed the first MI, See Supplementary Table 5 for more details.

Costs and health related quality of life

Unit costs used to estimate the mean costs are presented in the Supplementary Table 6. Incremental c~~C~~ost-utility ratios are not presented since the intervention was not clinically effective. The mean cost of the ProLife intervention was ZAR 2601 (SD 6) ($180.02 (SD $0.42)) per participant in the intervention arm (n=283). The mean cost of usual care was ZAR 681 (SD 357) ($47.13 (SD $24.71)) in the intervention arm (n=122) versus ZAR 706 (SD 302) ($48.86 (SD $20.90)) in the control arm (n=131). The total mean cost of care including the intervention was ZAR 3285 (SD R357) ($227.37 (SD 24.71)) in the intervention arm (n=122). EQ-5D-3L data were available at the 3 time points for 137 intervention and 159 control arm participants. The mean QALYs estimated over six months were 0.442 (SD 0.061) in the intervention arm versus 0.430 (SD 0.074) in the control arm (adjusted mean difference 0.006 (95% CI -0.001 to 0.013)).

DISCUSSION

This RCT did not ~~fin~~provided~~d~~ evidence for improved TB treatment success rates in those receiving the ProLife intervention compared to those receiving usual care. We could also ~~There was also~~ not demonstrate significant beneficial effects on any of the secondary outcomes, i.e., smoking, alcohol consumption, medication adherence and ART initiation. To our knowledge there are no other published studies of similar complex interventions that aim to improve TB treatment outcomes in patients who smoke or drink to harmful or hazardous extent. Interventions evaluated by other studies were either complex interventions or ~~complex~~ SMS-based interventions aimed at improving TB outcomes through the pathway of increasing adherence, but without an alcohol or smoking intervention component (43,44) or ~~or~~ focused on a single behaviour, namely smoking or drinking.(45,46). Of the latter studies, a brief smoking cessation intervention was effective in inducing smoking cessation in ~~TB~~ patients with TB but did not improve TB outcomes.(45) Conversely, in another study in India, intensive counselling for alcohol disorders led to significantly better TB treatment outcomes in the intervention group compared to the control group.(46) Smoking cessation also led to better TB treatment outcomes in a secondary analysis of a large tobacco

cessation trial in ~~TB~~ patients with TB in Bangladesh and Pakistan.(47) Our non-significant result for smoking-related outcomes is not consistent with findings from our previous TB study, which used a single MI session and found that the chance of sustained smoking cessation was twice as high in the MI intervention group compared to the control group,(14) albeit with a less stringent exhaled CO cut-off point. Evidence on the effectiveness of MI for smoking abstinence in non-TB settings has been equivocal.(48) Self-reported alcohol consumption decreased with about 4 points in both intervention and control arms in our study at both follow-up times. Answering questions on drinking in brief intervention trials may alter subsequent self-reported behaviour~~.(51)~~: e~~E~~xposing non-intervention control groups to an integral component of the intervention may therefore underestimate the effect of the intervention.(49) There have been few previous studies looking at MI and SMS interventions for the modification of hazardous/harmful drinking in the context of TB. A previous trial of a brief counselling intervention to reduce alcohol consumption in patients with TB did not find a significant effect on alcohol reduction.(50) Outside a TB setting, results have been mixed. A meta-analysis showed a small but significant improvement in outcomes when MI was used in conjunction with cognitive behavioural therapy for co-morbid alcohol use and depression.(51) Self-reported TB and ART medication adherence was high overall in our~~this~~ study population, which is consistent with other studies conducted in South Africa.(52,53) It is possible that we did not find a difference in treatment adherence due to a ceiling effect.

There were several key strengths in this RCT. This was an individually RCT with a relatively large sample size and a high follow up rate (87%) for the primary outcome. Primary outcome assessment was blinded. This was a novel intervention, which built on previous successes with both MI and mHealth interventions and was aligned with the WHO's call to increase the use of digital technologies to improve TB care.(15) We utilized a validated alcohol consumption questionnaire (AUDIT) (29) and a four-day timeline follow-back for medication adherence to reduce recall bias as self-reports tend to underreport drinking while overestimating adherence behaviour compared with.(54) (35) Smoking cessation was confirmed with exhaled CO using strict cut-off points. Overall, the quality of the counselling was acceptable. The results of our MI analyses suggest that the LHWs trained as counsellors were more proficient in MI than during the feasibility stage, as observed by their global rating scores on cultivating change talk, softening sustain talk, partnership and empathy. (Supplementary Table 4) These results were achieved by ongoing monitoring and training of LHWs during the trial and adapting the training based on feedback from the feasibility stage. Extra counsellors were also appointed to minimise travel distances to clinics. There were some limitations associated with this RCT. Trial recruitment had to be terminated before the planned sample size

because of funding and time constraints. Nevertheless the calculation of sample size was based on an anticipated 25% LTFU for the primary outcome, while in reality only 13.4 %, of the TB outcomes were not available. As a result, we achieved a slightly higher power to detect the a 10% difference in primary outcomes, than we had aimed for (83% vs. 80%). The smaller sample size did however reduce the power to detect a difference for secondary outcomes for which the LTFU was much higher than 25%. Also, the calculated sample size was not powered for subgroup analysis which was the case for outcomes relating to smoking, drinking, ART and cure rates. In addition, due to COVID-19 lockdown in March 2020, we had to switch to telephonic follow-up of participants using a shortened questionnaire (22 participants) and could not access clinics to retrieve outstanding TB treatment outcomes. The low intervention uptake meant that half of the participants received only one or two MI sessions combined with SMS messages. SMS messages were only used for the first half of the study period, and one quarter of participants did not receive their messages, a commonly occurring problem in developing countries.(20,55) It could be argued that in the absence of ongoing text messages, the MI and associated text messages were not enough to keep participants focussed for the second three months of the trial. The 2-arm study design did not permit the untangling of the individual effects of SMS and MI. Understanding their separate effects could have important cost implications as SMS-communication would be cheaper and easier to organise than individual counselling.

The lack of effectiveness of our intervention ~~consisting of three sessions of MI combined with SMS~~ on the primary outcome (TB treatment success) can have a number of possible explanations. Although intervention uptake was high (80.2%) for the first counselling session, many participants did not return for the second (29.7%) and third (47%) sessions. As a result of this only about half of the intervention arm participants received all three MI sessions. Furthermore, about one quarter of all participants did not receive any SMS-messages. Low intervention uptake leads to a dilution of any potential effects. ~~There were a number of possible technical barriers to SMS delivery: invalid phone numbers, phones that are off for a long duration of time, numbers that are deactivated, and phones that are disconnected from the network leading.(41) The proportion of participants with TB treatment outcomes recorded was high, but follow-up rates at 3- and 6-months were low. Due to COVID-19 lockdown, we had to switch to telephonic follow-up of participants using a shortened questionnaire (22 participants) and could not access clinics to retrieve outstanding TB treatment outcomes.~~

The lack of effectiveness on TB treatment success could~~may~~ perhaps also be explained by the complexity of the ProLife intervention itself: counsellors had to address multiple behaviours, namely medication adherence, tobacco smoking and hazardous/harmful drinking. ~~This integrated approach was nevertheless adopted to avoid the need for multiple vertical counselling services (in addition to TB treatment and HIV treatment), to allow the different elements of the programme to reinforce one another, and to improve the affordability, feasibility and acceptability for a future roll-out of the programme.~~ Despite having established the feasibility and acceptability of this approach ~~,~~(31) and ongoing on site performance monitoring and feedback of counsellors, it is possible that MI for multiple behaviour change in the ProLife study was counterproductive as counsellors may have ended up not focusing on any of the behaviours at optimal levels. Similarly, patients might have found it difficult to change multiple behaviours simultaneously, especially because smoking and drinking are mutually reinforcing. This integrated approach was nevertheless adopted to avoid the need for multiple vertical counselling services (in addition to TB treatment and HIV treatment), to allow the different elements of the programme to reinforce one another, and to improve the affordability, feasibility and acceptability for a future roll-out of the programme. It is also possible ~~There is some indirect evidence~~ that sequential interventions may be better, at least for smoking cessation.(56) More intensive counselling (more sessions) or a modified counselling method ~~with or without MI~~ may have been more appropriate, even more so since a recent review of reviews of MI casts doubt on its efficacy.(48,57,58) For example, m~~, m~~ore emphasis on increasing patient knowledge in addition to increasing self-efficacy may have been more effective.(59) The cause of the mobile health message delivery problems (such as poor network coverage, no electricity to charge phones) (60) would need to be investigated in order to increase the effectiveness of future mHealth interventions. Messages may also have to be intensified or modified to be more interactive and/or tailored to specific circumstances of each individual. This would improve the personal value of the intervention to the individual, which is likely to increase the chances of their participation in the intervention.(61) Consistent with the normalisation process theory,(62) cognitive participation in the intervention might have been higher had we been deliberate in the implementation to ensure the TB nurse who would have routinely seen the participants, provided additional support and motivated participants to attend MI sessions with the counsellor. In this way, the intervention would have gained 'legitimacy' but this would have led to unblinding of the nurses to the intervention arm.

In conclusion, ~~Th~~we could not demonstrate that the ProLife intervention was ~~is RCT provided evidence that the ProLife intervention was not~~ effective in ~~modifying the primary o~~ improving TB

treatment outcomes. This may be due to the lack of effect of the intervention, but ~~r~~ the study may also have been underpowered for the intermediary secondary outcomes~~econdary outcomes~~. Valuable lessons were learnt on challenges relating to training LHWs in MI counselling and delivery, ~~the~~ SMS-delivery in a challenging socio-economic context and the reasons for loss to follow-up of TB participants with multiple health problems. Further research is needed to provide answers on how to increase intervention uptake in poor resource settings and whether our complex intervention should have been more intensive ~~(with several sessions for each behavioural problem)~~. Other important questions are whether another counselling method would have been more effective. Lastly, in the light of the already existing evidence of SMS and the costs and implementation challenges relating to MI, intervention studies limited to an mHealth intervention but using different intensities, duration and type of interventions (oneway, twoway, interactive) are needed.

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Contributors

GML has led on study design and manuscript preparation and contributed to the monitoring of the study implementation. MK contributed to study design and the manuscript, led on the sample size determination and did the statistical analysis. NKM contributed to study design, particularly with respect to development of the MI intervention, did the analysis of the MI data and contributed to the manuscript writing. AVZ led the data management and SMS-system, monitored data quality and contributed to data analysis and manuscript writing. ASM contributed to study design and led on the preparation of the manuscript. NDM contributed to study design, intervention development and manuscript preparation. JL and SP led on the economic evaluation. AT contributed to the economic evaluation. JT was site lead for the Bojanala sub-district. OBO was site lead for the Sedibeng sub-district. MOB contributed to study design, data interpretation and the manuscript. KS and OAA are co-principal investigators. Both contributed to study design, data interpretation and manuscript writing. All authors read and approved the final draft of the manuscript.

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Competing interests

OA Ayo-Yusuf, the principal investigator, received a research grant (MRC-RFA-02: TB -05-2015) which was allocated to Sefako Makgatho Health Sciences University to pay for the expenses related to the research project. As co-prinicipal investigator K Siddiqi received part of the MRC-Newton research grant (MRC-RFA-02: TB -05-2015) which was allocated to the University of York to support the research by the authors affiliated to the University of York (K Siddiqi, ND Mdege, M Kanaan, S Parrot, J Lee). Goedele Louwagie received a small monthly remuneration per month from 1 October 2018 until 30 June 2020 as academic research coordinator. André van Zyl was employed as a research data manager on a part-time basis from 1 September 2017 and 30 June 2020. OA Ayo-Yusuf received support for attending meetings and for travel by Tax Justice Network Africa. He is the Vice Chair of the Standing Committee on Health, Academy of Science, SA (not remunerated). The remaining authors declare no competing interests.

Ethical considerations

This study received ethics approval from the Research Ethics Committees of: Sefako Makgatho Health Sciences University (SMU; Ref: SMUREC/D/234/2017: IR); the South African Medical Research Council (with the SMU Ethics Committee serving as the Research Ethics Committee Record); the University of Pretoria (Ref: 434/2017); the University of Witwatersrand (M160455); and the University of York (no reference number, approval date 15 January 2017 (29).

Patient Consent for publication

Not applicable

Data aAvailability statement~~of data and material~~

The study protocol was previously published (ImPROving TB outcomes by modifying LIFE-style behaviours through a brief motivational intervention followed by short text messages (ProLife): study protocol for a randomised controlled trial). The de-identified participant and SMS data sets are stored in labelled Stata files and are accompanied by a statistical analysis plan and metadata explaining each variable. Although data can be

viewed immediately, data will be embargoed for data analysis until 30 June 2023. Thereafter, permission must be obtained from the principal investigators (OA and KS) for any data analysis not yet performed by the primary research group. Data are stored in the institutional data repository at Sefako Makgatho Health Sciences University called Discover research (https://smu-za.figshare.com/) with a CC-BY 4.0 (Attribution) license (Creative Commons — Attribution 4.0 International — CC BY 4.0). The statistical analysis plan are available as supplementary material.

~~Data are stored in the institutional data repository at Sefako Makgatho Health Sciences University called Discover research (https://smu-za.figshare.com/). Data access will be embargoed until 30 June 2023.~~

Open access

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Trials

STUDY PROTOCOL Open Access

ImPROving TB outcomes by modifying LIFE-style behaviours through a brief motivational intervention followed by short text messages (ProLife): study protocol for a randomised controlled trial

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Abstract

Background: South Africa is among the seven highest tuberculosis (TB) burden countries. Harmful lifestyle behaviours, such as smoking and alcohol, and poor adherence to medication can affect clinical outcomes. Modification of these behaviours is likely to improve TB treatment outcomes and has proven possible using motivational interviewing (MI) techniques or use of short message service (SMS) text messaging. There have been no studies assessing the effect of combined MI and SMS interventions on multiple lifestyle factors and TB treatment outcomes.

Methods: This is a prospective, multicentre, two-arm individual randomised controlled trial looking at the effectiveness and cost-effectiveness of a complex behavioural intervention (the ProLife programme) on improving TB and lifestyle-related outcomes in three provinces of South Africa. The ProLife programme consists of an MI counselling strategy, delivered by lay health workers, augmented with subsequent SMS. We aim to recruit 696 adult participants (aged 18 years and over) with drug-sensitive pulmonary TB who are current smokers and/or report harmful or hazardous alcohol use. Patients will be consecutively enrolled at 27 clinics in three different health districts in South Africa. Participants randomised individually to the intervention arm will receive three MI counselling sessions one month apart. Each MI session will be followed by twice-weekly SMS messages targeting treatment adherence, alcohol use and tobacco smoking, as appropriate. We will assess the effect on TB treatment success, using standard World Health Organization (WHO) treatment outcome definitions (primary outcome), as well as on a range of secondary outcomes including smoking cessation, reduction in alcohol use, and TB medication and anti-retroviral therapy adherence. Secondary outcomes will be measured at the three-month and six-month follow-ups.

Discussion: This trial aligns with the WHO agenda of integrating TB care with the care for chronic diseases of lifestyle, such as provision of smoking cessation treatments, and with the use of digital technologies. If the ProLife programme is found to be effective and cost-effective, the programme could have significant implications for TB treatment globally and could be successfully implemented in a wide range of TB treatment settings.

Trial registration: ISRCTN Registry, ISRCTN62728852. Registered on 13 April 2018.

Keywords: Tuberculosis, Smoking, Alcohol, Motivational interviewing, Anti-retroviral therapy, Adherence

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Background

South Africa has the second highest incidence of tuberculosis (TB) and the sixth highest TB burden of the 30 high TB burden countries. It also has a high prevalence of human immunodeficiency virus (HIV) co-infection in patients with TB and a high mortality in these co-infected patients relative to most other high-burden countries [1]. In addition to HIV co-infection, a range of social, psychological and economic factors influence treatment success in TB. Of these, tobacco smoking and hazardous or harmful alcohol use are specifically mentioned in the South Africa National TB Management Guidelines [2]. Tobacco use and problem drinking are prevalent in TB patients, often co-occur [3–5] and are known to increase the risk of death and poor treatment adherence and outcomes [6–9].

As well as increasing the risk of TB infection and progression of disease [10], smoking is also known to increase the risk of treatment failure [11], relapse [12, 13] and death [14], and is associated with resistance to isoniazid, one of the main antimicrobials used to treat TB [15]. There is evidence that patients who stop smoking have better TB treatment outcomes and, if co-infected, better HIV treatment outcomes than current smokers [16–18]. In addition, alcohol misuse is associated with poorer TB outcomes through a range of mechanisms including decreased effectiveness of medications used to treat TB (including drug resistance), increased recurrence and treatment default rates and social marginalisation [3]. It has been estimated that 10% of the global burden of TB is attributable to alcohol use [19, 20].

Poor adherence to TB medication and anti-retroviral therapy (ART) significantly increases the risk of adverse effects and death in TB patients. Strategies are needed to improve medication adherence in TB-HIV co-infected patients, in whom integration of TB and HIV care has been shown to decrease mortality [21].

A number of studies have attempted to evaluate the effectiveness of tobacco cessation, alcohol reduction or TB treatment adherence interventions in TB patients [21, 22], but few have assessed the effect on TB treatment outcomes [23, 24]. We know that brief smoking cessation interventions, ranging from opportunistic advice and proactive telephone support through to in-person behavioural support over multiple sessions, are effective and affordable in low-income countries, in both TB patients and smokers in the general population [25, 26]. We also know that disease diagnosis could constitute a 'teachable moment', when people are more amenable to advice and motivated to modify harmful lifestyle behaviours [27]. For this reason, it is likely that patients receiving a TB diagnosis may be more successful in quitting smoking and moderating alcohol use if offered behavioural support, compared with smokers and problem drinkers in the general population.

Motivational interviewing (MI) is a counselling technique known to facilitate behaviour change [28], which has demonstrated effectiveness for the reduction of hazardous drinking, tobacco cessation, and TB treatment and/or ART adherence [19, 29, 30]. Our group has had previous success in achieving sustained smoking abstinence in TB patients through a brief MI intervention delivered by lay health workers (LHWs) [31]. There is also evidence to suggest that adherence to ART [32] and possibly TB medication [33], as well as tobacco cessation, can be enhanced with the use of short message service (SMS) text messages on mobile phone technology [34]. To our knowledge, no study has used MI in combination with SMS text messages to address multiple harmful behaviours that adversely impact TB outcomes.

The ProLife programme is a novel complex behavioural intervention targeting tobacco smoking, problem drinking, and TB and HIV medication adherence in patients with TB. This is the study protocol for the randomised controlled trial (RCT) aiming to assess the effectiveness and cost-effectiveness of the ProLife programme in improving TB treatment outcomes in primary healthcare clinics located in high TB-burden communities in three provinces in South Africa (Gauteng, Free State and North West). The protocol has been written in accordance with the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) guideline.

Methods/Design

Objectives

The primary objective is to assess the effectiveness and cost-effectiveness of the ProLife programme compared to usual care in improving pulmonary TB (PTB) treatment outcomes. We also aim to assess the effectiveness and cost-effectiveness of the programme in achieving abstinence from smoking, reducing harmful and hazardous drinking, and improving TB and ART medication adherence.

Trial design and setting

This is a pragmatic, prospective, multicentre, two-arm, parallel, individual RCT taking place in 27 purposively selected primary care clinics with the highest TB caseload in three districts in South Africa: Welkom in the Free State; Bojanala in the North West province; and Sedibeng in Gauteng province. To be eligible for inclusion in the trial, TB clinics had to be under the control of the provincial or local government (i.e. not a mining TB clinic). The intervention will be delivered by LHWs and three district coordinators who will each cover 1–2 clinics.

Participants will be randomly allocated to one of two arms:

Arm 1: Intervention arm – participants in the interventions arm will receive the ProLife programme;
Arm 2: Control arm – participants will receive usual treatment and support provided to TB patients in TB treatment clinics in South Africa ('usual care').

Intervention

The ProLife programme is a complex behavioural intervention aimed at improving treatment outcomes in TB patients who smoke tobacco, drink alcohol at harmful or hazardous levels, or do both. The ProLife programme has been developed in line with the Medical Research Council (MRC) guidance on developing and evaluating complex interventions [35] and has undergone a period of development and feasibility testing in South Africa. The paper reporting the results of this evaluation has not yet been published. The conceptual framework used to develop the ProLife programme assumes that smoking cessation, reducing harmful alcohol use and improved adherence to TB and HIV treatment will result in improved TB treatment outcomes.

Participants randomised to the intervention arm will receive three brief MI counselling sessions, lasting 15–20 min, each one month apart, from a trained LHW at their TB clinic. In the initial MI session, occurring at the start of TB treatment, the counsellor will establish the participant's tobacco smoking habits and problem drinking; potential obstacles and facilitators for medication adherence or treatment initiation (both TB treatment and ART) will be determined. The participant will determine which factor should be prioritised (i.e. agenda setting), which could be a plan either to quit tobacco smoking, reduce or quit drinking or deal with barriers relating to ART or TB medication adherence. 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 will focus on the previous agenda before moving on to the next behavioural problem (tobacco, alcohol or medication adherence) where applicable. The third session will deal with the last identified problem.

The individual counselling sessions will be re-enforced with SMS text messages regarding information, motivation and behaviours (IMB) supporting tobacco cessation, alcohol use and medication adherence. Text messages will be delivered twice a week over 12 weeks. All participants will first receive 10 TB-related messages. These messages will be followed by seven alcohol or smoking-related messages depending on whether the participant smokes or drinks. Co-joint users will receive all sets of messages (i.e. 24 in total).

Comparator

Participants in the second group are the controls and will receive usual TB treatment and support offered to TB patients. Control participants are seen by a TB nurse and receive the same biochemical investigations and medical treatments as the intervention arm. However, they will not receive the MI and SMS package of care as described above. Usual care also includes HIV testing with pre- and post-test HIV test counselling by a lay counsellor or a nurse (this varies by district).

In addition, health education is given on:

- nature of TB, treatment adherence, treatment side-effects/complications, drug interactions, tobacco use, alcohol use and other substance abuse. This is mostly done by the TB nurses, is not intensive and is educational in nature rather than a form of counselling;
- healthy diet by a dietician where possible;
- social problems and family support for treatment by a social worker as needed and depending on the availability of social workers; and
- point of care blood glucose, haemoglobin and pregnancy tests are performed. If co-infected with HIV, a full blood count, liver function test and creatinine are also carried out.

Participants

The inclusion criteria for participants are:

- adult patients (aged ≥ 18 years) with drug-sensitive (bacteriologically or clinically confirmed) PTB;
- initiating TB treatment or on TB treatment for < 1 month (these include both 'new' and 'retreatment' patients);
- current smokers and/or hazardous/harmful drinkers who are not alcohol dependent (Alcohol Use Disorders Identification Test [AUDIT] score ≥ 8 for men or ≥ 7 for women but < 20);
- access to a functional mobile phone; and
- understands one of the four languages used for the trial (Sesotho, Setswana, Isizulu or English).

Exclusion criteria:

- alcohol-dependent participants (AUDIT score ≥ 20);
- Extrapulmonary TB without PTB; or
- Resistance to one or more TB drugs at baseline (because drug-resistant TB needs further investigations which take several months and is treated through

a long, specialised treatment programme if present).

Recruitment process

Participants will be recruited consecutively from the starting date of the trial until the required sample size for each clinic has been achieved. The sample size per clinic will vary depending on the workload for each clinic. TB patients who initiate treatment (or who have been on treatment for < 1 month) will be asked if they would like to participate. If they agree, they will then be screened for eligibility by trained fieldworkers immediately after the TB nurse at the clinic has initiated TB treatment and started the routinely used TB treatment record. Eligibility screening will involve being assessed in line with the inclusion criteria listed above and being asked about their:

- smoking status: using the Global Adult Tobacco Survey [36] questionnaire, patients will be asked whether they currently smoke daily, less than daily or not at all, and in the past daily, less than daily or not at all. As TB patients in South Africa often smoke little or may not have smoked for a few days because of ill-health and the word 'current' is open to interpretation (particularly when translated); 'current' has been defined as smoking daily and non-daily in the last four weeks for the purpose of this study. Smoking habits will be further quantified at baseline interview;
- current alcohol usage: AUDIT, a validated tool for identifying problem alcohol behaviours [37], will be used to quantify alcohol intake. Those with an AUDIT score ≥ 8 for men or ≥ 7 for women but < 20 will be eligible for the trial.

If eligible, patients will be invited to join the trial. For those who wish to be enrolled into the trial, written informed consent will be obtained (Additional file 1).

Randomisation and allocation

Patients will be randomised using a randomised sequence generator performed by the trial statistician (MK) who will remain blind to the arm allocation. We will use block randomisation with varying block sizes stratified by the clinic to achieve equal numbers in intervention and control groups within each clinic (see the 'Sample size' section). Allocation concealment will be done with consecutively numbered, sealed, opaque envelopes.

Ethics and consent

Potential participants will be approached and given an introduction to the study and basic eligibility criteria required for participation. Participants who meet the eligibility criteria for language, age, PTB, treatment duration and mobile phone access will be given a consent form (Additional file 1) to sign before screening for alcohol and tobacco use eligibility as the alcohol-related questions are sensitive and the fieldworkers must access the patient treatment record. If recruited to the trial, participants will be ask to consent to enter the trial, including consent for audio recording of the MI counselling sessions (Additional file 1). A witness signature will be required where the participant is unable to read or write.

The identity of participants will be protected by allocating each participant a unique trial number, which will be used on all research documents and will ensure anonymity for the data analysis. Participation will be voluntary; participants will be informed of their right to withdraw from the study at any time without giving a reason for their withdrawal. The project is unlikely to be directly harmful to TB patients with the exception of inconvenience in terms of time spent on the counselling sessions. Participants will receive ZAR 60 (US$4.19) travel and other expenses reimbursement for each MI counselling session and follow-up visit related to the study.

Timeline and procedures

Figure 1 Additional file 4 outlines the overall participant flow through the trial. Eligible and consenting patients will be enrolled in the trial and the baseline interviewer-administered questionnaire and record review completed. Participants will receive a baseline interview on the same day as the recruitment or on the nearest available date suitable to both the participant and the LHW. The initial part of the questionnaire covers socioeconomic and demographic factors. We will also assess for depression using the CES-D10 [38], a validated tool, as depression may be a potentially moderating or mediating factor affecting treatment outcome. See Additional file 2 for the full case report form (CRF).

The next part will cover medical history, particularly TB and HIV history and current medications. Participants identified as current smokers at eligibility screening will be asked more in-depth about their smoking habits and quit history. All participants will be asked about their use of smokeless tobacco and exposure to second-hand smoke. Participants will also be asked about time and money spent on TB-related healthcare visits in the past three months and health-related quality of life (see the 'Economic evaluation' section). After administering the baseline interviews, fieldworkers will draw the allocation envelopes and organise the follow-up sessions for the participants. Each of the interviews on health status, tobacco and alcohol use at

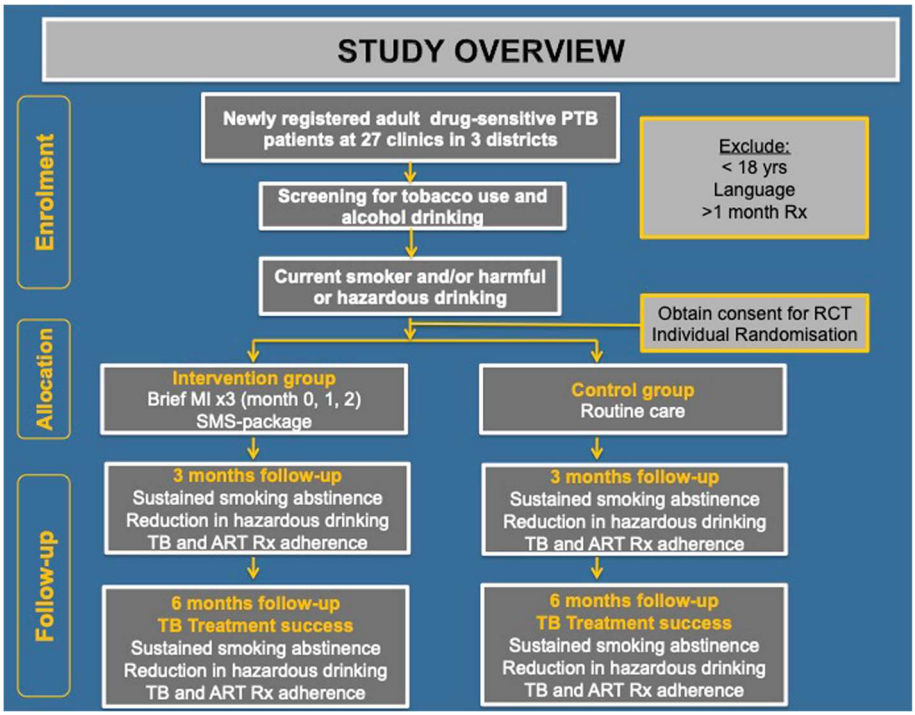

Fig. 1 CONSORT Flow diagram outlining randomisation and participant recruitment

baseline, three months and six months is not expected to last > 25 min.

Primary outcome

The primary outcome is TB treatment success at 6–9 months of follow-up, measured using the routinely collected programmatic TB treatment outcomes as defined by the World Health Organization (WHO) and adopted in South Africa. This is a binary variable defined as either successful treatment (cured or treatment completed) or failed treatment, death, acquired drug resistance, loss to follow-up or 'default', or not outcome evaluated. Table 1 defines the different treatment outcomes according to the South African Department of Health National Tuberculosis Management Guidelines [2].

Individual TB treatment records will be used as the primary source of information. The TB treatment record is the routinely used clinical document initiated by the TB nurse when the patient first presents at the TB clinic and includes demographic information as well as a comprehensive overview of the patient's treatment over time. The TB treatment outcomes will be obtained 6–9 months after the TB treatment start dates. This is to allow for short periods of treatment interruption and time needed to confirm the TB treatment outcomes status. For example, the TB nurse may have to wait for end of treatment TB sputum or culture results or time may be required to determine whether a participant died. In some cases, TB patients may also undergo a longer TB treatment regimen.

Routinely reported outcomes will be verified for correctness by checking the actual individual diagnosis and treatment records. For example: if the outcome is classified as cured, then the criteria for diagnosis and outcome definitions should have been adhered to. Attempts will be made to verify the information of patients classified as 'defaulted' or who are lost to follow-up by contacting them telephonically or sending them a short text message. Sputum cultures and smears will be performed at baseline, two months, three months and six months per routine care.

Secondary outcomes

The following outcome measures will also be recorded at the six-month follow-up:

- sputum conversion at the end of treatment: this will be measured by negative culture or smears in the group of participants who had bacteriology confirmed PTB at baseline, i.e. cure rates in intervention group versus control group for participants who initially had sputum AFB-positive, culture-positive or GeneXpert-positive PTB;
- six-month continuous smoking abstinence: the Russell Standard defines continuous abstinence as a self-report of not smoking > 5 cigarettes from the

Table 1 Definitions for TB treatment outcomes according to the South African Department of Health National Tuberculosis Management Guidelines

Treatment outcome	Definition
Cure	Patient in whom baseline smear or culture was positive at beginning of treatment AND is smear/culture negative in the last month of treatment and on at least one previous occasion at least 30 days prior According to local protocol, a patient who is diagnosed using Gene Xpert and is sputum negative for TB at 11 and 23 weeks is considered 'Cured'.
Treatment completed	Patient whose baseline smear or culture was positive at the beginning and has completed treatment but does not have a negative smear/culture in the last month of treatment and on at least one previous occasion > 30 days prior. Patients diagnosed with PTB whose baseline smear (or culture) result was negative and who started treatment based on clinical and radiological findings who have shown clinical improvement and completed the prescribed course of treatment. *N.B. The smear examination may not have been done or the results may not be available at the end of treatment.*
Treatment failure	Patient whose baseline smear or culture was positive and remains or becomes positive again at 5 months or later during treatment. Patients who were negative at baseline but were later found to be positive. *N.B. This definition excludes those patients who are diagnosed with RR-TB or MDR-TB during treatment.*
Died	Patient who dies for any reason during the course of TB treatment.
Treatment default	Patient whose treatment was interrupted for two consecutive months or more during the treatment period.
Transfer out	Patient who was referred to a facility in another district to continue treatment and for whom the treatment outcome is not known.
Acquired resistance	Participants who are subsequently referred for MDR treatment.

start of the abstinence period (in this case, six months), supported by a negative biochemical test (exhaled carbon monoxide [CO] < 10 ppm) at final follow-up [39]. For the purpose of our study, we will, however, use a more stringent criterion of exhaled CO < 7 ppm, based on findings from our previous study that some participants who reported continued smoking had an exhaled CO < 10 ppm [26]. This analysis will be performed on the group of participants who were current tobacco smokers at baseline;

- reduction in harmful or hazardous drinking: alcohol use will be measured using the AUDIT questionnaire. The questionnaire will be administered at screening (which will take place on the same day or shortly after the baseline assessment) and again at three months and six months. Changes in the total AUDIT score will be used to compare change in drinking behaviour between control and intervention groups. This analysis will be performed on the group of participants who were harmful or hazardous drinkers at baseline.
- TB and ART medication adherence: adherence to both TB and ART medications will be measured using a modified version of the AIDS Clinical Trials Group (ACTG) Adherence Questionnaire. The questionnaire is a validated tool for measuring adherence specifically to ART and we will use an adapted version to also measure TB medication adherence [40]. Field workers will administer the baseline part of this questionnaire as part of the baseline CRF and adherence will be measured at both three months and six months.

Adherence will be measured using an adherence index calculated by the formula (using the four-day recall table):

[Total number of doses taken/Total number of doses prescribed] x 100

ART patients with at least 95% of adherence will be considered as having optimal adherence and those with < 95% will be considered as having low (or suboptimal) adherence. For the TB medication regimen, patients with at least 95% of adherence will be considered as having optimal adherence and those with < 95% will be considered as having low (or suboptimal) adherence:

- increase in proportion of HIV-positive participants on ART: HIV status will be recorded in the TB Treatment Record. HIV-positive participants will be asked about ART status at baseline, three months and six months using standardised questions on the CRF.

The following outcomes will be measured at three months:

- biochemically verified three-month sustained tobacco cessation;
- reduction in harmful or hazardous drinking;
- TB drug and ART adherence;

- increase in proportion of HIV-positive participants on ART.

The schedule for enrolment, intervention and assessments is presented in Fig. 2. Table 2 summarises the methods of data collection and analysis for each of the primary and secondary outcomes.

Data collection and management

Data will be collected and recorded by field workers equipped with Android phones with a mobile data collection application installed. MI counselling and data collection will take place in a well-ventilated private area inside or outside the clinic (but within the grounds of the health facility); MI sessions will be audio-recorded where consent has been obtained. Fieldworkers and LHWs will be provided with high particulate respirator masks to minimise the risk of infection.

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT	*-t*	0	*1m*	*2 m*	*3 m*	*6-9m*
ENROLMENT:						
Eligibility screen (including smoking status and baseline AUDIT)	X					
Informed consent	X					
Allocation		X				
Assigned trial ID and initial visit date		X				
INTERVENTIONS:						
The ProLife Programme		←	—	→		
Usual care		←	—	→		
ASSESSMENTS:						
Clinical review of TB treatment record	X	X				X
HIV Status		X				
ART status (if HIV-positive)		X			X	X
Smoking history	X	X				
Socio-demographic history		X				
Depression screen (CES-D10)		X			X	X
Record sputum culture, smear or Gene Xpert result		X		X	X	X
Smoking abstinence (self-report)					X	X
Smoking abstinence (Exhaled CO)					X	X
Repeat AUDIT					X	X
Modified ACTG					X	X
Economic evaluation		X			X	X

Fig. 2 SPIRIT Figure outlining data collection throughout trial

Fieldworkers will follow-up all participants in both arms at three and six months within a window period of two weeks before and two weeks after the ideal three-month and six-month visit. Participants will receive SMS reminders three days before each planned visit. Participants will also be in a position to send 'please call me' messages to the district coordinators, who will then call the participant to solve problems that may have arisen with the appointment.

The electronic data captured will be stored on secured and password-protected storage servers and mobile phones which ensure data privacy through only allowing authorised research staff access to the data. The electronic data collection system used for the study requires an SMS gateway to send and receive messages to the research participants. Consenting participants' phone numbers, participant IDs and associated SMS messages will be stored on the SMS gateway's secured and password-protected server.

Data quality will be ensured by providing fieldworkers with standard operating procedures (SOPs), training and ongoing support on the importance of data quality, data collection and data collection problem solving. Training will consist of a four-day session before the commencement of the pilot and a one-day training session focusing on problems identified during the pilot preceded the trial. The data manager will continuously monitor the captured data for missing variables and inconsistencies in order to resolve any data problems.

The data manager will export the data from the secured server, conceal the participants study arm allocation and de-identify the data before sharing the data in STATA and R compatible formats. The exported de-identified data will be stored in Dropbox, a secure cloud storage platform, for sharing with the lead trial statistician at the University of York for analysis.

All research data and documents referring to the ProLife trial will be stored and maintained in a secured storage space at SMU for a minimum of 15 years from the end of the ProLife trial. Study materials will be destroyed 15 years after the study.

Blinding and limitation of risk of bias

This is a complex behavioural intervention and the team dynamics mean that all team members work very closely with one another. As such, LHWs and participants cannot be blinded to the intervention. The determination of the primary outcome will be done by the TB nurses who are blinded to the intervention status of the participants based on routinely collected data. Blinding of the field researchers collecting other questionnaire data (Additional file 2)

Table 2 Summary of methods of data collection and analysis for primary and secondary outcomes

Variable	Method of data collection	Method of data analysis
Primary outcome: TB treatment outcome as defined by WHO and the South Africa TB Management Guidelines (see Table 1)	• CRF and TB treatment record • Treatment outcome as recorded by TB nurses in TB cards using the standard WHO definitions of cure, completions, failure, death, TB treatment interruption, drug resistance developed in course of treatment (confirmed for correctness by checking sputum culture/smear at baseline, at 5 and 6 months)	Binary outcome: successful (cured of completed) vs not successful (died, failure, treatment interruption, drug-resistant TB) All participants, excluding those transferred out
Secondary outcome: sputum conversion	• Sputum culture/smear at baseline, 5 and 6 months to determine cure rates for PTB patients who had a positive smear or culture at baseline • Sputum conversion at 2–3 months	Binary cured vs not cured for the subgroups of participants who had a positive smear/culture at baseline Binary conversion vs not for the subgroups of participants who had a positive smear/culture at baseline
Secondary outcome: change in smoking behaviour	• CRF – questions as per Russell's Standard – baseline smoking behaviours and then at 3 and 6 months • Exhaled carbon monoxide reading at 3 and 6 months	Binary outcome validated 3 and 6 months sustained smoking cessation for the subgroup of participants who were smoking at baseline
Secondary outcome: percentage reduction in harmful or hazardous drinking (change in AUDIT score)	• AUDIT score at baseline and at 3 and 6 months	Change in AUDIT score (continuous) for subgroups of participants who were hazardous or harmful drinkers at baseline
Secondary outcome: HIV and TB medication adherence	• CRF – questions modified from ACTG	Binary outcome (% adherent vs non-adherent)
Secondary outcome: proportion of HIV-positive participants on ART	• HIV status at baseline • ART status at baseline, 3 months and 6 months	Binary on ART vs not on ART for the subgroup of HIV-positive participants, taking into account baseline % on ART

will not be possible. The statistician will be blinded to the intervention or control arm allocation of participants during the analysis stage.

There is a potential of biased outcome reporting on self-reported tobacco smoking or alcohol consumption favouring the intervention arm. This will be minimised by training the fieldworkers in open communication and standardised data collection. Tobacco cessation will also be verified by exhaled CO monitoring. Given the use of the TB treatment record as a primary source of information pertaining to TB outcomes, there is a risk of non-differential misclassification. However, this risk is equal in both the treatment and control arms and therefore the decision has been taken that the TB treatment record can be used as a primary data source (i.e. bias would be towards the null).

Sample size

The sample size has been set at 696 participants (348 participants per arm). This sample size is sufficient to detect a 10% difference in TB treatment success rates (0.86 vs 0.76) in the ProLife group versus the control group with 80% power, a significance level of 0.05 and 25% attrition. The sample size per clinic was in the range of 14–74 participants per clinic with a median of 24. The assumed success rates in the control group are based on actual success rates in TB patients in the studied provinces.

Statistical analysis

We will summarise baseline data descriptively by trial arm; however, we will not undertake statistical comparisons. For continuous measures, we will report means and standard deviations (SD); for skewed data, we will also provide medians and interquartile ranges. For categorical data, we will report counts and percentages. For the primary outcome, we will conduct analysis on an intention-to-treat basis. We will use binary logistic regression to compare the main outcome between the intervention and the usual care arm.

We will carry out similar analyses for the secondary outcomes with appropriate regression techniques: logistic regression for categorical outcomes and linear regression for continuous outcomes. We will also adjust for baseline characteristics and other covariates (HIV status, sex, alcohol versus tobacco versus both, district) if these differ between trial arms at baseline.

In case of missing data, we will employ a number of methods including multiple imputations to assess the sensitivity of the results. We will conduct subgroup analyses to determine whether TB treatment outcomes differ between subgroups, as follows: HIV-positive versus HIV-negative participants; participants with an alcohol problem only versus smokers only versus participants who are conjoint smokers and drinkers; and participants who were GeneXpert positive versus participants who were GeneXpert negative at baseline.

We will follow the CONSORT statement guidelines in reporting. We will use the statistical packages STATA and R to carry out the analyses and a P value < 0.05 will be considered as statistically significant. The statistical analysis pertaining to cost-effectiveness will be described in the section detailing the planned economic evaluation.

Monitoring

Each centre will be responsible for its own data entry and local trial management. Monitoring and site training will be carried out at each site within specified intervals. The project manager will visit each district every third month with the counselling supervisor. The district coordinators will visit each clinic bi-weekly; the site leads and data manager will visit the sites when required.

The monitoring will adhere to the principles of Good Clinical Practice and will follow an agreed monitoring plan. During their bi-weekly visits, the district coordinators will be guided by a checklist to confirm adherence to protocol, review eligibility verification and consent procedures, and provide additional training as needed. Any adverse events will be formally recorded and reported where appropriate.

The mobile data collection tool was improved based on findings from the pilot phase and feedback from the field staff capturing the data. Validation was added to the mobile questionnaires to ensure that all questions should be answered, participants only answer question relevant to them and that no unusual values (range checks) are entered. Coordinators can use the mobile data collection tool on their phones to monitor incomplete data activities, outstanding and upcoming appointments with participants and basic project performance indicators per clinic.

The data captured during the interviews with the participants are only captured on the electronic mobile data collection tool and can therefore not be verified by the site coordinators. However, the district coordinators will require access to all (enrolled TB) patient medical records including, but not limited to, laboratory test results and prescriptions. They will do spot checks by comparing the captured data with the medical records and look for missed outcomes reporting: verify completeness; consistency; and accuracy of data being entered on CRFs. The site leads (or delegated personnel) should work with the district coordinators to ensure that any problems detected are resolved.

The data will also be checked by the data manager for missing or unusual values (range checks) and checked for consistency within participants over time. If any such problems are identified, the individual centres will be contacted and asked to verify or correct the entry.

Indicators related to enrolment, premature withdrawal, motivational interviewing completion, CRF completion and SMS delivery will be analysed and included in monthly reports.

As the ProLife programme is a low-risk intervention, the decision was taken not to appoint an external data monitoring committee.

Training and intervention fidelity monitoring

Eighteen LHWs, three district coordinators and one person who will be focusing on counselling supervision underwent MI training over five days, which covered: basic knowledge of TB; treatment adherence; tobacco and alcohol use; overview of the overall spirit of MI and communication style; core interviewing skills; evoking change talk, hope and confidence; developing a change plan; and strengthening commitment. The LHWs' knowledge in terms of TB, alcohol use, tobacco smoking, TB and ART treatment adherence, and motivational interviewing was assessed before and after the training

To ensure that all the essential steps, techniques and skills of an MI session are covered during each session, the LHWs will be provided with a checklist to use during each session (Additional file 3). At the end of each session, they will also complete a post-session semi-structured form onto which they will indicate the extent to which they implemented each element of MI, as well as their general qualitative impressions of that particular session.

During the trial, the LHWs will receive regular supervisory support from the district and national study coordinators. In addition, an appointed supervisor with proficiency in MI will be providing monthly counselling supervision to the LHWs in each site, by travelling to each of the three sites and then providing support to the LHWs in a group, followed by individualised support to each LHW separately. All lay counsellors completed grade 12 and have at least one year of prior counselling experience in TB and/or HIV.

In order to assess the fidelity of the counsellors' delivery of motivational interviewing during the trial, the validated Motivational Interviewing Treatment Integrity Coding Manual 4.2.1 (MITI) tool will be used [41]. We will tape record each LHW's counselling sessions and then randomly select 5% of each counsellor's patients and then use the recordings of all three sessions with those patients for the MITI task. Those selected recordings will be transcribed and translated into English. Two independent raters who are Setswana/Sesotho speakers will listen to the recordings and code a randomly selected 20-min portion of the written transcript. In the case of shorter counselling sessions, the entire recording will be assessed. The coding will entail making 'Global Ratings' (on four dimensions: Cultivating change talk;

Softening sustain talk; Partnership; and Empathy) and 'Behaviour Counts' (with respect to the items: giving information; persuade; persuade with permission; question; simple reflection; complex reflection; affirm; seeking collaboration; emphasising autonomy; and confront). A score will be assigned to each of these items and the scores compared against the competency and proficiency thresholds that are specified in the MITI manual.

Economic evaluation

The economic evaluation will be a within-trial incremental cost-effectiveness analysis of the ProLife package over and above usual care conducted alongside the RCT. In each arm of the trial, we will estimate the costs of delivering the intervention to participants. Costs consist of the delivery of ProLife intervention (staff costs, overheads and consumables) in the intervention arm and the costs of behavioural support and support (staff time, overheads and consumables) in the control arm. Costs will be calculated based on the length of time of contacts and the unit cost of the healthcare worker delivering the intervention. These costs should demonstrate some within patient variability as cost will be partly dependent upon the length of the recorded appointments.

We will also record contacts with health services for TB by patients in each trial arm, using the questionnaires adapted from those used in a previous trial of TB [42]. Applying unit costs of healthcare to quantities recorded in the service use questionnaire will produce a healthcare cost profile for each patient at baseline, three-month and six-month follow-ups. Healthcare cost profiles based on TB contacts can then be used to investigate differences in total costs between the treatment and control groups. The base case analysis will use healthcare costs as the study perspective. This is justified by presenting the cost implications of delivering the ProLife intervention from a healthcare decision maker's perspective. However, we will also record participants' travel costs associated with making the journey to the intervention site. This will estimate the wider societal cost to patients associated with receiving treatment.

We will estimate the cost per additional successful TB outcome by computing an incremental cost-effectiveness ratio (ICER) combining treatment and wider healthcare costs with outcome data from the trial. The analysis will also use measures of health utility. We have registered on the EuroQol website to use the country specific version of EQ-5D-3 L for South Africa to measure health-related quality of life at baseline, three-month and six-month follow-ups. We will use EQ-5D-3 L to estimate changes in quality-adjusted life years (QALY) using the area under the curve by using the utility score at each time point to create a profile [41]. A cost utility analysis is then performed by combining incremental health outcomes using QALYs with the incremental cost. The cost utility analysis will estimate the cost per QALY that estimates the value for money afforded by administering the ProLife intervention over and above usual care. We will plot incremental cost against incremental outcome using a cost-effectiveness plane. We will also conduct sensitivity analyses to assess the robustness of the ICER and use bootstrapping techniques to calculate cost-effectiveness acceptability curves. Supporting analysis will also present the costs to patients incurred by making visits to both trial arms to present the wider cost burden. However, these costs will not be included in the base case scenario as the objective is to present the value for money from the perspective of the purchaser or commissioner.

Discussion

Ending the TB epidemic is one of the Sustainable Development Goals (SDG) established by the United Nations. The WHO calls for a 90% reduction in TB incidence by 2030 compared to 2015 and has highlighted the need for intensified research and innovation. The WHO has recently published guidance advocating the use of digital technologies, specifically mobile text messaging campaigns, in the treatment of TB as a means of improving the provision of patient-centred care and supporting medication adherence [43]. This publication highlights advances in mobile technologies and network coverage as opportunities to more effectively support patients during what can be a long period of treatment. This study is well-aligned with this guidance and, to our knowledge, this is the first trial looking at a complex behavioural intervention aiming to use MI techniques, alongside SMS, to modify a range of harmful lifestyle factors with the aim of improving TB treatment outcomes.

Work already undertaken in the formative phase suggests that the ProLife intervention is feasible and acceptable to patients. However, we anticipate some potential procedural challenges throughout the trial as we recognise that patients with TB may feel unwell and have taken steps to ensure that the MI and data collection are as brief and comfortable for patients as possible. The district coordinators will call participants to follow-up with those who missed appointments.

Implementing complex interventions in the real world can pose logistical challenges and careful process evaluation will be required to fully understand the challenges that may be presented. However, there is evidence to suggest that using MI techniques can be cost-effective when implemented in healthcare settings and the ProLife programme could represent a scalable and feasible approach to improving the care of patients with TB globally. Its scalability is particularly relevant in South

Africa as the government plans to formally introduce community health workers as part of its health workforce.

Trial status

Protocol Version 1.2, 5 January 2018. Recruitment ongoing; piloting started at 30 clinics: 7 May 2018 and was completed by 31 August. The actual trial enrolment started on 13 November 2018. We expect to enrol the target sample size by May 2019 and plan to continue with follow-up until December 2019. The trial was piloted internally from May 2018 until the end of August 2018; piloting results will be reported at a later stage, together with the trial results.

Additional files

Additional file 1 Participant consent form for screening and for trial. (DOCX 94 kb)
Additional file 2 Case report form. (DOCX 58 kb)
Additional file 3 Counselling Activities Reporting Form. (DOC 103 kb)
Additional file 4 SPIRIT Checklist. (DOC 120 kb)

Abbreviations

ACTG: AIDS Clinical Trials Group; ART: Anti-retroviral therapy; AUDIT: Alcohol Use Disorders Identification Test; CO: Carbon monoxide; CRF: Case report form; EPTB: Extra-pulmonary TB; HIV: Human immunodeficiency virus; LHW: Lay health worker; MI: Motivational interviewing; PTB: Pulmonary TB; SADHS: South Africa Demographic and Health Survey; SMS: Short Message Service; TB: Tuberculosis

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Authors' contributions

ASM contributed to study design and preparation of the manuscript. GML led on study design and contributed to intervention development and preparation of the manuscript. NDM contributed to study design and intervention development. NM contributed to study design, particularly with respect to development of the MI intervention. JT is site lead for the Bojanala sub-district. OBO is site lead for the Sedibeng sub-district. MOB contributed to study design. MK contributed to study design and led on the sample size determination and statistical analysis plan. AT contributed to the planned economic evaluation. SP contributed to study design and led on the planned economic evaluation. KS and OAA are co-principle investigators. All authors read and approved the final draft of the manuscript.

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Availability of data and materials

The data sharing plans for the current study are unknown and will be made available at a later date. Research results will be published in international indexed journals and disseminated to managers of the provincial and national Departments of Health. Furthermore, the provincial and national Departments of Health will be involved in the design and final evaluation of the project so as to assure their ownership, sustainability and scaling the programme beyond the life of the trial.

Ethics approval and consent to participate

The trial has received approval from the Research Ethics Committees of Sefako Makgatho Health Sciences University (SMU; Ref. SMUREC/D/234/2017: IR), the South African Medical Research Council (with the SMU Ethics Committee serving as the Research Ethics Committee Record), the University of Pretoria (Ref. 434/2017), the University of the Free State (Ref. HSREC 71/2016), the University of Witwatersrand (M160455) and the University of York (no reference number, approval date 15 January 2018). The protocol has gone through full external peer review throughout this process. In the case of any protocol amendments, these will be submitted to the SMU Ethics Committee for approval. Managerial approval has been obtained from the provincial and/or district managers to conduct the study at clinics in Bojanala district (North West Province), Lejweleputswa district (Free State province) and Sedibeng district (Gauteng province). Informed consent will be obtained from all study participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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