

ASSIST Pakistan: Action to Stop Smoking In Suspected Tuberculosis in Pakistan

An intervention to stop tobacco use among patients suspected of TB – evaluation of an integrated approach

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1. Abstract

1.1. Background

There is a strong causal link between tobacco use and tuberculosis incidence. Almost 20% of the total disease burden due to tuberculosis is attributable to tobacco use. Pakistan is one of the top ten high burden countries for both tuberculosis and tobacco use. Therefore, in such countries it is desirable to deliver smoking cessation interventions integrated within TB control programmes. However, there is a lack of evidence on the effectiveness and cost-effectiveness of such approaches.

We carried out a cluster randomised controlled trial to assess the effectiveness and cost-effectiveness of delivering smoking cessation interventions in achieving six-month continuous abstinence among adult smokers who are suspected of pulmonary tuberculosis.

1.2. Methods

33 health centres (1957 participants) were randomised to three arms: (a) intervention arm I - behavioural support *plus* bupropion; (b) intervention arm II - behavioural support only; and (c) control arm - usual care and a self-help leaflet. Patients in all three arms were assessed for abstinence (verified by Carbon Monoxide test), one and six months after the quit date. To account for clustering, results were analysed using mixed-effects (multi-level) logistic regression.

1.3. Findings

A total of 42.1% (275/654) of those offered behavioural support and bupropion achieved six months' abstinence compared with 39.8% (254/639) offered behavioural support alone, and 7.9% (52/656) offered usual care and a self-help leaflet. Both treatment conditions led to significantly improved abstinence rates relative to usual care (OR=16.3, 95% CI: 5.6-47.8, and OR=15.4, 95% CI: 5.2-45.2 for the behavioural plus pharmacological support condition and behavioural support condition respectively). After adjustment for potential confounders the effect measure estimates increased for both behavioural plus pharmacological support (OR=22.8, 95% CI: 7.3-71.4) and behavioural support alone (OR=20.6, 95% CI: 6.5-64.5). An approximate ICER for behavioural support plus bupropion was \$91.51 and for behavioural support alone was \$9.13 per smoking abstinence.

1.4. Interpretation

Behavioural support is effective in promoting cessation in smokers in Pakistan with suspected tuberculosis. Adding bupropion does not appear to increase abstinence rates.

2. Key words

Abstinence

Pakistan

Randomised controlled trial

Smoking

Tobacco

Tuberculosis

3. The research problem

Tuberculosis (TB) and tobacco use, considered to be two ‘colliding epidemics’, lead to 1·8 and 5·4 million deaths worldwide per year respectively. There is a strong causal link between tobacco smoking and TB incidence: exposure to tobacco smoke increases the risk of TB infection (OR 1·8; 95%CI: 1·5–2·1) and of developing TB disease (OR 2·6; 95%CI: 2·1–3·4). TB patients who smoke tobacco deteriorate more rapidly and have higher mortality (RR 2·6; 95%CI: 1·8–3·6) than non-smoking TB patients; and tobacco smoking is also associated with higher TB treatment default rates, treatment failure, and relapse after treatment completion. Approximately 20% of the total disease burden due to TB is attributable to tobacco use, which, based on current smoking trends, is predicted to lead to an extra 18 million TB cases and 40 million TB deaths between 2010 and 2050. Moreover, since low- and middle-income countries (LMICs) account for almost all TB cases, and smoking prevalence is often higher among TB patients than the general population (studies have shown that in South Africa, 56% of people with active TB smoke; in India, 71% of new TB patients smoke; and in Malaysia, 40% of new TB patients smoke), a moderate increase in TB prevalence will have a high impact on TB mortality there.

The causal link between tobacco and TB suggests that addressing tobacco use within TB control is likely to be beneficial for controlling TB (as well as preventing chronic diseases). The WHO proposes integrating smoking cessation within TB programmes. Exploratory studies carried out in Sudan, Malaysia and Indonesia highlight that such integration is feasible and potential beneficial. However, there is a need to establish a sound evidence-base for the effectiveness and cost-effectiveness of delivering smoking cessation interventions to patients coming in contact with TB programmes. There is strong randomised controlled trial (RCT) evidence for the use of behavioural support, nicotine replacement therapy (NRT), and other drugs such as bupropion and varenicline in smoking cessation. However, as far as we know, these interventions have not been evaluated in any LMIC in a RCT including patients suspected of TB.

We therefore developed a trial in Pakistan, which is among the 10 countries with the highest burdens of both TB and tobacco use. In Pakistan, 400,000 new TB cases are diagnosed and 58,000 patients die because of TB every year. Tobacco use, mainly cigarette smoking, is also highly prevalent: 33% of men and 4·7% of women are regular smokers. We estimate, based on attributable fractions, that among all deaths due to TB in Pakistan, 15% are due to tobacco. NRT and varenicline were not available in Pakistan at the time of designing this trial. Moreover, policy makers were interested in the effectiveness of behavioural support and the added value of bupropion to aid smoking cessation.

4. Aims and objectives

Our project's aim was to develop and evaluate a behavioural support intervention to reduce tobacco dependence among TB suspects. We carried out this research in Pakistan (Figure 1) over a period of three years in four different phases. Each phase had a specific objective as follows:

- **Objective 1:** To help in identifying the likely behaviour change-elements in relation to tobacco use for the behavioural support intervention including the training package for professionals, and the education tool and information leaflet for patients.
- **Objective 2:** To assist in developing and piloting the intervention to allow us to refine and standardise it, test its feasibility in a resource-limited situation and test the feasibility of various (research and routine) data collection tools.
- **Objective 3:** To carry out a cluster randomised trial to assess the effectiveness and cost-effectiveness of the behavioural support intervention in achieving carbon monoxide (CO)-verified six-month continuous abstinence among adult smokers who were suspected of pulmonary TB. We compared three approaches: behavioural support plus bupropion; behavioural support only; and usual care plus a self-help leaflet (control). In Pakistan, health centres do not routinely offer any advice or educational materials to aid smoking cessation. However, given the overwhelming evidence of smoking cessation interventions in general, we offered a self-help leaflet as an absolute minimum in the control arm.
- **Objective 4:** To carry out a subsequent qualitative study to identify barriers and facilitators in delivering the intervention and identify key activities required in scaling up the intervention.

Tobacco Cessation Trial Sites

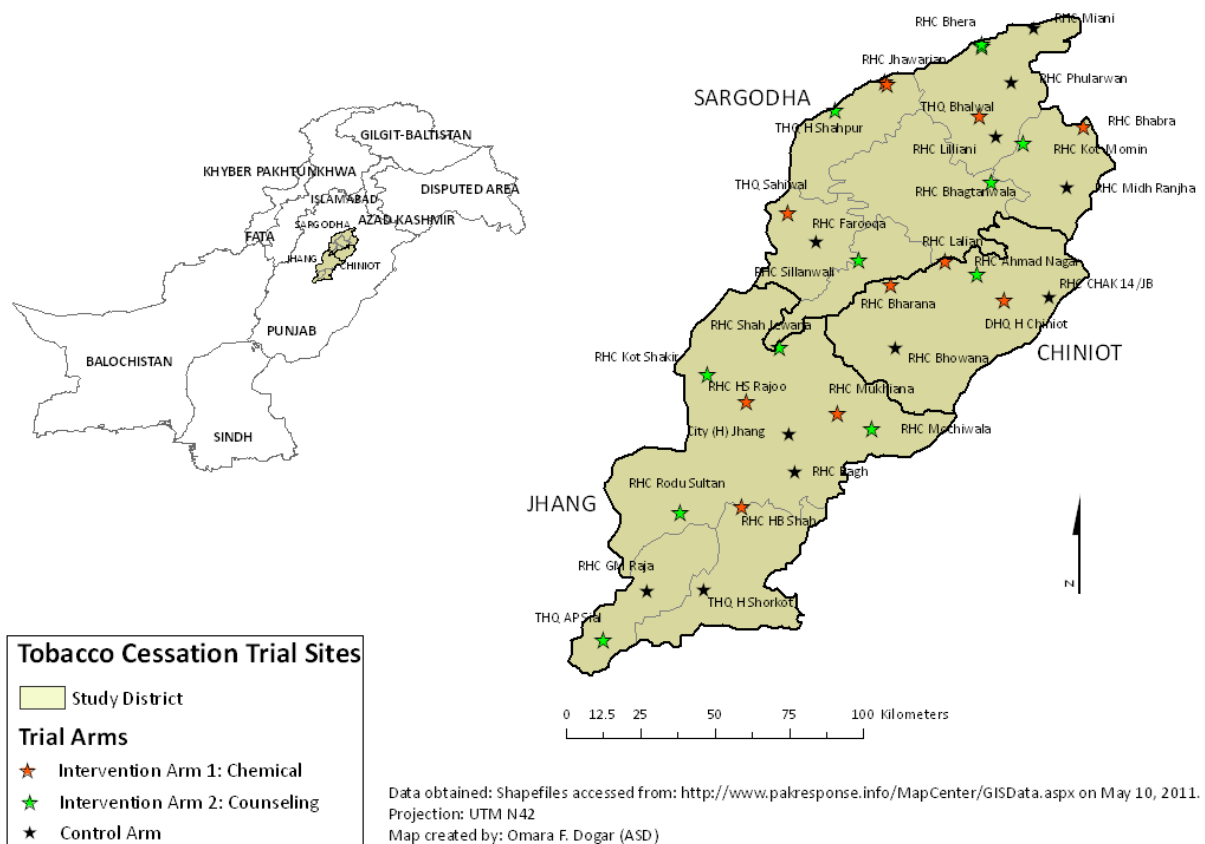


Figure 1: ASSIST Pakistan trial sites

5. Methodology

We proposed following methods to meet each of the above objectives as follows:

5.1. Objective 1

From a health systems point of view, we were interested in understanding the local health care context for delivering the intervention including issues like current working environment, staffing, and workload issues. We were also interested in exploring the possibilities of funding NRT and bupropion, their registration and addition to the essential drug list. We proposed to do this situation analysis through conducting a workshop with the Tobacco Control Programme and other stakeholders at the start.

We proposed to use qualitative approaches to understand: (a) the extent to which health professionals particularly doctors currently convey risks of tobacco use and benefits of its cessation to their patients; (b) how they perceive their own role, knowledge, skills and

confidence in conveying these messages; (c) how their own behaviour towards tobacco use is going to affect their attitude towards patients using tobacco and the advice they might offer; (d) which professional group would be most appropriate to provide the different elements of the package e.g. initial advice, motivation assessment, counselling, follow-up; and (e) what would be most useful form and content of training package and tools to support them in this process. Among patients, especially presenting to primary care with respiratory complaints, we were interested in understanding: (a) to what extent they currently understand the risk of tobacco use and benefits of its cessation; (b) in what form and detail they would like to receive such information from health professionals; (c) what kind of visual images will be evocative but also culturally appropriate if used in education materials; (d) what are their common misconceptions about tobacco use; and (e) what is their attitude towards smoking cessation aids including willingness to pay for NRT (f) do women and men respond differently to advice by physicians versus others, and by advisors based on gender.

We planned focus group discussions (FGDs) to identify common themes as these allow participants to interact with each other and stimulate and generate themes, which are sometimes not possible with interviews. We were not only interested in “what they say they do” (their belief system) but also in “what they really do” (their behaviour). FGDs are particularly useful in this context as participants often challenge each other and therefore provide more in-depth understanding of inconsistencies between reported and actual behaviour. We were also interested in the social and cultural constraints that modify behaviour. FGDs were conducted in health centres that were to be participating in the subsequent phases of the study. We planned to conduct two FGDs each from the following three categories of informants i.e. six in total. We invited 6-8 participants for each FGD from the following:

- Doctors
- Nurses and health technicians (paramedical staff)
- Patients (tobacco users) with respiratory symptoms (one with males and other with females)

Purposive sampling was used to understand the breadth of variation as well as the typical attitudes and behaviours among professionals and patients. We tried to have participants from similar social class and backgrounds to allow enrichment of the data with minimum censorship. FGDs were facilitated by the research officer who used a FGD topic guide, which was piloted with a group of health professionals and patients in another health centre. FGDs were tape-recorded. We conducted an inductive analysis by indexing through generating codes and identifying themes from the narrative text. Analysis was conducted in Urdu language to identify and link themes. All narratives were analysed separately first, followed by comparing and linking themes generated during the analysis.

5.2. Objective 2

These can be divided into development and pilot sub-phases.

5.2.1. Development

In the development sub-phase, two different processes were used to develop products for health professionals (training module & desk-guide) and patients (illustrative education tool & leaflet) respectively. We convened a “local working group” of national experts in tobacco control, primary care, health systems and district health services management, the district TB programme coordinator and primary care physicians and paramedics. This group agreed the form and contents of the training module and desk-guide. We asked a local professional media company to develop illustrative education tools and leaflet. We made sure that the education tools are prepared to be appropriate for both urban and rural population acknowledging different patterns of tobacco use and literacy. The product specifications were based on the outcomes of the FGDs. The final product were reviewed and approved by the local working group.

5.2.2. Pilot

In the pilot sub-phase, the intervention was delivered in six health centres (three urban, three rural). In these centres we introduced a questionnaires including queries such as: (a) current tobacco use (yes or no); (b) amount of tobacco use; (c) whether the patient is willing to try to stop tobacco use (yes or no); and (d) whether the patient has been registered to receive behavioural support intervention. We developed tools for registering in the trial. This included a patient card filled in for every tobacco user. 25 consecutive attendees who consented to participate and met the inclusion criteria were recruited in each centre (n = 100) and offered the intervention. Training evaluation of health professionals, in-depth interviews with patients and health professionals, and observations of the health professionals delivering intervention, were carried out to identify: (a) any structural or processes barriers to the implementation; (b) modifications required in the data collection tools and systems; and (c) any modifications required in the training package based on participant observation and training event evaluation; (d) any changes in the assigned roles of health professionals within the package; and (e) any modifications required in desk-guide, patient education tool and leaflets based on observation of care delivery and discussion with care providers.

We also estimated the validity of the subjective assessment of abstinence by using a Carbon Monoxide (CO) test on all participants at follow up during this pilot.

Ultimately, based on the results of this pilot, we developed a final version of the various components of the behavioural support intervention. We also modified the process for delivering the intervention as required.

5.3. Objective 3

ASSIST is a balanced cluster-randomised trial with three arms: (a) intervention I–behavioural support plus bupropion; (b) intervention II–behavioural support only; and (c) control–usual care plus a self-help leaflet.

5.3.1. Settings

The trial took place in 33 health centres (clusters) in the public sector in rural and urban settings in districts of Jhang and Sargodha in Pakistan. The only inclusion criterion for these centres was being registered as fully-functioning diagnostic centres by the TB control programme. All eligible centres were invited to participate in the trial.

5.3.2. Participants

Participants were recruited during June 2010 and February 2011. All patients suspected of pulmonary TB were requested to see the TB DOTS facilitators¹ to discuss possible participation in the trial. Patients aged ≥ 18 years, who regularly smoked cigarettes or other forms of tobacco (at least one cigarette/day), were suspected of pulmonary TB (cough for three or more weeks without any other cause) and who gave informed consent, were registered in the trial. Motivation to quit was not an explicit inclusion criterion. However, consent to participate in a smoking cessation trial where all arms offered some help would imply an implicit willingness to consider quitting. Patients who required hospitalisation or urgent medical attention were excluded.

5.3.3. Intervention – Behavioural support

Behavioural support (Table 1), offered in health centres allocated to intervention arms I and II, consisted of two structured consultations (initial enlistment was based on WHO’s “5 As Approach”). The aim of the first consultation was to assist a smoker who was willing to set a quit day (a week after the first contact) by encouraging them to see themselves as a non-smoker, planning for their quit day and preparing them for the initial stages of the quit attempt. The second consultation provided an opportunity for follow-up and review progress. The activities within each of these consultations were designed using behaviour change techniques, considered effective in smoking cessation.

Following necessary training, TB DOTS facilitators delivered behavioural support using an educational resource (flipbook) developed for this purpose. Other health professionals in these centres were also briefed about the intervention. The first consultation, lasting approximately 30 minutes, was an extension of the patient’s clinical visit, and the second

¹ TB DOTS facilitators are paramedics responsible for: (a) assisting in identifying, recording and reporting new TB patients; (b) educating them about TB; and (c) ensuring direct observation during the intensive phase of their treatment.

consultation, lasting approximately 10 minutes, was arranged for a week later coinciding with the quit day.

Table 1: Behavioural support intervention

<i>Activity</i>	<i>Purpose</i>
Consultation one: (prior to quit day) confirmation, planning and preparation	
Confirm that the smoker is aware of tobacco-related harm and would like to stop smoking	To confirm awareness of the health and financial consequences if he/she continues to smoke and to ensure that a smoker is quitting because he/she wishes to and is willing to commit to a quit day.
Smoking assessment	To ascertain how dependent a smoker is and to recognise his/her normal pattern of smoking
Preparing and planning to stop smoking	To work with the smoker in order to identify: (a) the times and situations which are likely to be more difficult during the quit attempt and; (b) coping strategies
Conclusion	To summarise the information given and reaffirm the quit day
Consultation 2: reflection (on quit day)	
Review tasks and coping strategies from previous week	To check that the smoker has completed the preparation to quit and understands the strategies being prepared
Discuss withdrawal symptoms	To prepare the smoker for possible withdrawal symptoms that may jeopardise the quit attempt

5.3.4. Intervention - bupropion

In addition to behavioural support, patients in intervention arm I were also offered a seven-week course of bupropion free of charge. At first consultation, bupropion SR- 75 mg per day was given initially for a week, with the patient quitting on day seven of treatment; 150 mg per day was prescribed for the following six weeks. Doctors and DOTS facilitators received guidance on using bupropion. At the second consultation, patients were also asked about any side effects and treatment concordance.

5.3.5. Control

Patients in the control arm received usual care and a self-help leaflet. The DOTS facilitators in this arm only received instructions on trial procedures.

5.3.6. Follow-up

Patients in arms I and II were given follow-up appointments at one, five and 25 weeks after their first contact. Patients in the control arm were followed up at five and 25 weeks.

5.3.7. Outcomes

The primary outcome was continuous smoking abstinence six months after the quit day verified by expired CO measurement using a hand-held meter (Pico⁺smokerlyzer, Bedfont Ltd): patients were considered abstinent only if they had confirmed CO levels at or below 9ppm (Russell standard) at both one-month and six-month follow-up. This cut-off value has a sensitivity of 88% for cigarette smokers and 84% for all types of smokers, and a specificity of 84% for each. TB DOTS facilitators took these measurements at follow-ups. We cross-validated this information by getting research officers to phone randomly-selected participants (two per facility per month) and verifying if CO tests were carried out. The research coordinator also randomly phoned 5-10 patients per month to confirm the registration form entries and to verify if CO tests were carried out. Secondary outcomes included point abstinence at both one and six months.

5.3.8. Sample size

In calculating sample size, we took account of clustering, expected effect size, power, event rate and potential attrition rate. Based on the findings of relevant Cochrane reviews, we estimated that to have 80% power (at $P < 0.05$, two-sided) to detect a difference in six month continuous smoking abstinence of at least 10% between each of the intervention groups and the control group (which we estimated would have 10% continuous smoking abstinence), using an intra-class correlation coefficient (ICC) of 0.036 to allow for clustering (based on cluster-RCTs conducted in primary care), we would need a sample of 1320 smokers. Therefore, with 33 clusters (TB diagnostic centres) – 11 in each arm of the trial – we required a sample of 40 patients per cluster. However, to allow for up to 20% attrition rate at six months (as seen in a feasibility study in Sudan), we set out to recruit a minimum of 50 patients per cluster.

5.3.9. Randomisation

Health centres were randomly allocated using a simple stratified randomisation procedure to achieve balance of Tehsil headquarter (THQs) health centres and rural health centres (RHCs) across the three trial arms by a researcher who was blind to their identity. THQs are situated in the urban parts of the district while RHCs are located in its rural parts. There are some rural/urban differences in smoking prevalence (20.7% in urban and 22.0% in rural areas) and patterns (cigarette smoking is more common in urban areas while hookah² is more common in rural areas) which justified the above strategy(17). The allocation sequence was generated using computer-generated random number lists.

² An oriental smoking pipe with a long tube passing through an urn of water that cools the smoke as it is drawn through. It is also known as hookah, shisha, narghile, water pipe, hubble-bubble pipe and qalyan

5.3.10. Statistical analysis

Data was analysed in accordance with the consolidated standards for reporting trials (CONSORT) guidelines and its extension to cluster randomised trials. All analyses were performed using SAS 9.2 (Cary, NC; USA). Outcomes were analysed on an intention-to-treat basis. All loss to follow-up was imputed, assuming that those for whom we did not have complete follow-up data remained smokers. No other imputations were carried out, as the loss to follow-up was only 5.5%. Ancillary analysis on complete cases is also presented.

Univariate distributions and frequencies were examined to identify covariates and to categorise continuous variables (e.g. age and income) and re-categorise categorical variables (e.g. type of smoking). ‘Smoking form’ varied: some participants only smoked cigarettes, some smoked both cigarettes and hookah and some only hookah. We acknowledge differences in the composition and volume of smoke inhaled between a cigarette and a hookah ‘session’. However, in order to avoid complexity, we combined the two variables i.e. the number of cigarettes smoked and/or number of times hookah smoked.

Multi-level analyses were conducted at the individual level to account for clustering at the level of health centre. We analysed the effect of each of the interventions on the primary and secondary outcomes with mixed-effects (multi-level) logistic regression using generalized linear mixed models for non-linear data in SAS (PROC GLIMMIX), which use all the available data to yield unbiased estimates of variables for mixed effect models when outcomes are missing at random, using a linearization estimation technique. All analyses accounted for clustering through the PROC GLIMMIX random intercept statement: the random-effects portion of these models provides the structure needed to account for clustering or potential lack of independence that may exist between individuals for the same health facility.

We also estimated an approximate incremental cost-effectiveness ratio (ICER) using ICER tables described in a recent paper using the incremental cost of the intervention (based on staffing and material costs) and the effect size obtained for the intervention.

5.4. Objective 4

At this stage we required an in-depth understanding of the way intervention was implemented. We were interested in factors that acted as barriers to effective implementation and how health professionals overcame these. We were also interested in the key drivers in the system, which were instrumental to successful implementation in certain health centres. We were interested in understanding the extent to which patient felt supported in their efforts to stop tobacco use through the health service intervention; which factors motivated them to quit; and which constrained them. We preferred to use semi-structured interviews and FGDs with key informants (see below) to gain this

understanding. We recruited groups of study participants from two health centres in each trial arm that performed above and below average respectively.

Following six Health Facilities (2 in each arm; 1 with highest tobacco smoking abstinence rate and 1 with the lowest) were selected for this purpose;

Intervention Arm1: RHC Jahwarian (0.07); RHC 104 NB (0.65)

Intervention Arm 2: RHC Ahmad Nagar (0.11); RHC Bhera (0.72)

Control: City (H) Jhang (0.00); RHC Phularwan (0.37)

Participants included:

- Patients who were offered intervention and did not quit smoking
- Patients who were offered intervention and quit smoking
- Doctors and programme managers
- Other paramedical staff.

We used an interview topic guide and a FGD guide to collect data. All communications were tape-recorded and transcribed. We used a sequential FGDs and analysis process so that the later FGDs could be informed by and test themes emerging from the earlier FGDs. Data was categorised and coded for a thematic analysis. Data was organised to identify key themes. Dependability of these themes was also checked with respondents.

To promote and support long term implementation of behavioural support intervention, we sought the national TB and Tobacco control programmes' endorsements for the intervention and planned to work with them to start scaling up the intervention.

6. Project Activities

These are as follows:

6.1. Objective 1

6.1.1. Meetings/Workshops with Stakeholders

We carried out two activities in this regard

- A workshop with TB programme managers
- A meeting with tobacco control programme manager and the WHO lead

Workshop

A workshop was conducted in January 09 with TB programme managers (two provincial leads), senior management team at ASD (including ex-director of malaria control programme, lead for Global Fund for TB, ex-dean of the Institute of Public health, Lahore, Pakistan), representatives from Nuffield Centre and Leeds PCT. The aim was to develop a shared understanding of the local health care context for delivering the tobacco

cessation intervention. During this workshop, participants; (a) agreed on the scope of the intervention; (b) discussed the existing care pathway of patients suspected of TB; (c) understood various components of WHO's 'five steps to quit' model; and (d) identified appropriate points in the pathway where different components of WHO's model might be feasible. Participants also discussed the existing roles; responsibilities and workload issues of health professionals in TB programme and highlighted who might be best suited to deliver different components of the intervention. Participants agreed on the following recommendations:

- The intervention will be limited to patients using tobacco in the form of inhalation (cigarettes, Hookah, bidi). The chewing tobacco users will not be included as the health education materials and messages would be very different from inhalational tobacco.
- Since all patients suspected of TB, contact the laboratory at the diagnostic centre, the laboratory technician can best assess the eligibility for the study. Sufficient training and display materials ought to be provided to these technicians at all participating centres.
- TB DOTS facilitator appears to be best suited to deliver most components of the intervention. However, he/She would need supervision and support from the medical doctor in the centre.
- The medical officer at the centre is best suited and qualified to assess and prescribe patients with tobacco cessation treatment

Participants also discussed the training requirements of the various health professionals who could be potentially involved in the delivery of the intervention, follow up arrangements and the need for various resources for participating patients.

The issue of willingness to pay for the treatment was also discussed with TB control programme managers. Given the overwhelming evidence that links tobacco use with TB, there was full support for tobacco cessation activities to be carried out within the TB programme. There was also support to deliver the behavioural support intervention by the TB programme health professionals. There was also an interest to find out the cost-benefit of bupropion in Pakistan context in addition to the behavioural support intervention. However, there was no commitment to fund bupropion by the TB programme in the long term.

Meeting with Tobacco control leads

A representative from ASD, Nuffield Centre and Leeds PCT met with the Tobacco control programme manager and the WHO lead for tobacco control for Pakistan. The aim of this meeting was to develop a shared understanding of the objectives, delivery, outputs and possible policy implications of this study. We also explored the possibilities of funding NRT or bupropion. Following key points emerged from the discussion.

- There was a clear support for the aims and objectives of the study from tobacco control programme side. There was also a general approval of the overall plan of action and mode of delivering the intervention within the TB programme.
- It was acknowledged that tobacco control programme in Pakistan is in infancy. The initial government funding has helped in establishing a central policy unit and a strategic direction for the programme. Programme is committed to smoking cessation interventions. Programme is in the process of developing a national strategic plan, which will address cessation interventions in more detail. However, there is no infrastructure or resources to deliver tobacco cessation at present. Therefore, the idea to deliver smoking cessation integrated within TB programme was well supported.
- Nicotine replacement therapy (NRT) is available in certain pharmacy outlets in Pakistan. However, this is imported directly from the UK and therefore, is relatively expensive. It would not be possible to fund NRT in its imported form and therefore should not be considered in the trial at this stage.
- Bupropion is locally manufactured and therefore available in Pakistan at a reasonable cost. Currently there are about 25 million smokers in Pakistan. The per person cost of Bupropion (agent being used in pharmacotherapy) is about Rs: 1100. Total estimated cost for a universal coverage would be about Rs: 27,500 million. Programme is keen to arrange bupropion/ or alternate drugs for pharmacotherapy of as many as possible number of individuals participating in smoking cessation. However, providing universal coverage to all smokers will not be possible for the national programme at this stage. Tobacco control programme is interested in learning about the cost-effectiveness of delivering both behavioural support intervention and Bupropion within TB programme in Pakistan context. It was also agreed that learning about cost-effectiveness of Bupropion in addition to the behavioural support intervention would be beneficial as currently there are no resources to fund such treatment within the programme.

6.1.2. FGDs with users and beneficiaries

As part of the qualitative research component of the “Tobacco cessation trial in TB suspects”, we carried out a total of seven FGDs between January 16th and March 3rd, 2009.

Composition of FGDs

The participant composition of the FGDs conducted is as follows:

- Two groups consisting of doctors who are involved in the management of patients with tuberculosis in health centers and TB hospitals,
- Two groups of DOTS Facilitators (paramedical staff) who are involved in management of TB patients in RHCs
- Three patient groups:
 - One group of young male patients (under the age of 25 years)

- One group of older male patients (over the age of 25 years)
- One group of adult female patients (over the age of 18 years)

Description of participant groups

• *Medical FGDs*

The two doctor FGDs were carried out in the districts of Rawalpindi and Sargodha.

The FGD in Rawalpindi included 10 doctors of various seniority (Medical Officers & Senior Medical Officers) working in the different Rural Health Centers (RHCs) of the district. These doctors are actively involved in the management of patients with tuberculosis at their respective health facilities. The FGD was carried out during one of the quarterly district TB meetings held at the District TB Coordinator's office. The age range of the doctors varied from 30 years to 52 years.

The FGD carried out in Sargodha district included 7 doctors (Medical Officers & Senior Medical Officers, and two pulmonology specialists) working in different Rural Health Centers as well as the district TB hospital. The age range of the doctors varied from 35 years to 55 years. The FGD had special blend of the doctors involved in TB treatment and management.

• *DOTS Facilitator (paramedical) FGDs*

Similarly, the two paramedical FGDs were carried out in the same districts (Rawalpindi and Sargodha) where the medical FGDs were conducted. The DOTS Facilitators' main roles include the counseling and follow-up of patients with tuberculosis attending their health facilities.

The FGD in Rawalpindi included seven DOTS Facilitators working in different Rural Health Centers of the district. The FGD was carried out at one of the quarterly District TB meetings held in the District TB Coordinator's office. The age range of the health staff varied from 24 years to 55 years. The FGD in Sargodha district was composed of seven DOTS Facilitators working in different Rural Health Centers as well as the district TB hospital. The age range of the health staff varied from 23 years to 56 years.

• *Patient FGDs*

1. *Young male patient group (Age < 25 years)*

The FGD was conducted in Bagha Sheikhan, a small village in a rural part of Rawalpindi. The participants included young men below the age of the 25 years. Most were Potowari-speakers (a dialect of Punjabi). Their occupations included daily wage earners, welders, a steel fixer, salesman and shopkeeper.

2. *Older male patient group (Age > 25 years)*

This FGD was also conducted in Bagha Sheikhan. It was held at the rural health center located there. Participants were older men above the age of the 25 years. Most of them were Potowari-speakers, and their occupation profile included daily wage earners, steel fixer, salesman, tobacco factory worker and shopkeeper.

3. Female patient group

This FGD was conducted in Bagha Sheikhan at the local rural health center. The participants included young women above the age of 18 years. Most of them were Potowari speaking (a dialect of Punjabi).

Findings

Following themes emerged from these FGD. Full details are available in the attached output.

- Lack of patient understanding and awareness
- Patient motivation for initiating and continuing use of tobacco
- Patient perception of risk of personal harm from tobacco use
- Patients' receptiveness to health messages
- Importance of contextualizing health messages
- Visibility of and social acceptability of tobacco use
- Willingness to pay
- Perceived importance of tobacco cessation advice and intervention
- Current practice and barriers encountered
- Health professionals' knowledge, confidence and skills
- Tools and media for delivering tobacco cessation interventions

6.1.3. Intervention development

Based on the feedback from the FGDs, it was suggested by participants that any intervention developed should consider the following:

- There is a general consensus of the negative attributes of tobacco use by both patients and health staff. However, there is a lack of patient understanding of the risks of tobacco use or an awareness of the treatment options available.
- Patients were willing to receive health messages from both paramedical and medical staff alike, regardless of gender.
- The visibility of tobacco use confers a degree of social acceptability that needs to be counteracted by more visible anti-smoking material. In particular, health facilities could adopt smoke-free policies, and health care staff could avoid using

tobacco in front of patients. This would help create an environment not conducive to tobacco use.

- DOTS Facilitators are well suited for providing counseling, as this is a key role for them in the existing TB control programme. As such, they are the focal health professionals providing counseling to TB patients, and have the skills and experience to do so.
- However, medical input is also required with regards to the prescribing of any drug therapies. The DOTS Facilitators do not feel confident providing drug treatment to the patients independently.
- In addition, although the doctors had a heavy workload, they were willing to provide a brief health message. The paramedical staff felt that the sensitization of the patients to health messages by doctors was crucial. If this was not done, they feared that patients would not be as receptive to their health advice.
- Additional training for the DOTS facilitators as well as supporting health promotion materials would help them deliver the tobacco cessation message more effectively.
- At follow-up appointments, the difficulties encountered by patients attempting to quit need to be explored and patients provided with coping strategies and advice on how to deal with these difficulties.
- A structured proforma for nicotine assessment was universally asked for.
- Medical staff also expressed a need for treatment guidelines and information on the indications and contra-indications for the drug treatments.
- Health messages needed to be contextualised and relevant for the target population locally. Furthermore, the messages would need to be in a language and medium accessible to patients who may have low literacy levels.
- Tobacco cessation messages needed to be more visible for patients.
- Greater use of visual imagery would help improve patients' perception of risk of tobacco use and may galvanise some to attempt to quit.
- Patients were willing to pay for treatment, provided the duration of therapy was short, the treatment effective, and the total costs of treatment did not exceed what they were already paying for tobacco.

6.2. Objective 2

6.2.1. Development of smoking cessation intervention

We developed four products as part of the smoking cessation intervention

- Patient education tool (Flip Book)
- Patient education leaflet
- Pharmacotherapy guidelines

- Training package

Their development took place as follows

Patient education tool (Flip Book)

A patient education tool (Flip Book) was developed to facilitate the care provider in communicating, counselling and registering patients for smoking cessation. The Flipbook has sketches/illustrations that are designed to face the patient and related written text that faces the provider while communicating the messages.

Patient education leaflet

To reinforce the information to the patients (from their interaction with the care provider in the intervention), they are also provided with the leaflets. These leaflets contain information on the hazards of the tobacco smoking, benefits of quitting it and what the patient can do to quit smoking.

However two different types of leaflets were designed for this purpose; one for the control arm and one for the two intervention arms. For the control arm, a narrative type of approach was used for the leaflet; whereas for the intervention arms the leaflet is designed with revision of the visual information of the Flip book and behavioural support intervention. For the Intervention arms leaflet, the “triggers” and the “with-drawl effects” that influence the patients are clearly identified. Patients are guided to deal with them using pictorial messages.

Pharmacotherapy guidelines

In addition to the above materials, the doctors in the Intervention arm 1 (Bupropion + behavioural support) was provided with the pharmacotherapy guidelines to help them in understanding its dosage schedule, adverse effects of the pharmacotherapy and its contraindications.

Training package

The training package (manual) was designed for single-day training for health care providers in the study. The learning objectives of the course were that, at the end of the course, participants would be able to:

- Use Flipbook to administer behavioural support intervention with patients suspected of TB.
- Administer CO test and interpret test results
- Fill in and update the ‘Patient Registration Form’

6.2.2. Development of additional tools for the trial

Data collection tool for research

The data collection tool for the research is called “Tobacco registration Form”. In addition, a monthly register for each health facility was also maintained to record monthly registration of the patients registered in trial, including their smoking status.

Data collection tool for monitoring

A system of monitoring and supervision was established to make the process of registration fool proof and for quality control during data collection. The field supervisors and research assistants were to monitor the activities in the field by visiting the health facility according to the approved schedule from research coordinator. The “Health facility monitoring guidelines” and the checklist of activities that the research assistants were supposed to do in their routine health facility visits were mentioned in detail in the operational guidelines. This included checking the supplies (drugs, registration materials, etc), the health care staff availability, as well as the data collection process itself. In addition the issues that arose during the registration were discussed in monthly meetings and the solutions identified are recorded.

6.2.3. Pilot Trial

We carried out following activities in this regard

Enabling of health facilities

The activities of the pilot were carried out in the existing health facilities of the Ministry of health primary health care network in District Sargodha. For the pilot phase of the study, we selected six health facilities (urban and rural locations). Two health facilities were selected for each one of the three trial arms. 25 patients were recruited in each of the health facility.

The required materials (patient registration forms, medicines [pharmacotherapy arm only], Flipbooks, leaflets, CO meters) were handed over to the Executive District Officer Health (in-charge of District Health Department). These were in turn supplied to the authorities in the health facilities to initiate the pilot trial.

Before starting the pilot, the health care providers (doctors and DOTS facilitator) identified in each health facility for the tobacco cessation activities, were given training on the activities to be conducted. Through this exercise, the health care providers were able to identify their roles, practice patient registration and use the Flip book, leaflets, CO meter, pharmacotherapy guidelines and other materials/processes to be involved in study.

Subsequently, the research coordinator and the research assistant observed the registration process in the health facilities (2 days/health facility). The research coordinator provided practical support to the health care providers in the areas where they had difficulties or perceived and delivered the intervention inappropriately.

Patient recruitment, advice, treatment and follow up

Patient recruitment in the health facility for the pilot started from September 1, 2009. Patients coming to the outpatient departments in the health facility and fulfilling the eligibility criteria for the trial were requested to visit the DOTS facilitator to seek their consent and enrol them in the trial. Patients who consented were enrolled in the trial and were delivered the behavioural support intervention using the Flip book. Their details were recorded in the registration form. During the intervention, brief advice on harms of tobacco smoking was given. Subsequently, their dependence on tobacco and motivation to quit was assessed. Following this, patients who were willing to quit were helped to develop a plan for quitting and managing their triggers for smoking. The patients' CO meter test was performed and the readings recorded on the registration form. Patients in the pharmacotherapy arm were referred back to the doctors, who assessed them for prescription of medicine. After completion of the activities, patients were informed about the time/day of next follow-up and were requested to report back to the health facility.

Patients in the intervention arm 1 and 2 were followed up at the end of week 1. On this visit, patients were assessed for any with-drawl effects, their experience of managing the triggers and for pharmacotherapy arm the patients were enquired about any adverse effects to the medicines. CO meter was used to test and report the CO reading in patient's breath.

For control arms, the first follow up was at the end of first month. Patients were asked about their smoking status and their CO test was performed. For intervention arms 1 and 2, the 2nd follow up was carried out at 1 month. Patients were asked about their smoking status and their CO test was performed. For pharmacotherapy arm, patients were enquired about any adverse effects to the medicines.

Use of CO meters to validate outcomes

We took the advice of smoking cessation specialists in the UK and used CO meters to validate the outcomes instead of cotinine testing. The CO meter can detect if the person has been smoking in the last 24 hours and is used in the UK for research monitoring purposes. Since it does not require taking a sample and its transportation, CO meter assessment was considered as appropriate, feasible and reliable method of assessment.

Monitoring and supervision

A three level system for monitoring was designed for the tobacco cessation trial, in order to have quality assurance for data collection at the health facilities. These included the routine weekly health facility visits by the research assistant. A checklist of information (health facility visit monitoring form) was used to see if different aspects of supplies and registration are handled properly at the health facilities. The research assistant checked the responses on the registration forms filled for correctness and completeness. He recorded these in his health facility monitoring form. Research assistant also observed the registration process at the time of his visits and guided the health care providers about

any shortcomings in counselling and registration of patients. The research assistant also validated 10% of the registration forms (filled by the health care providers) of the health facility per week by contacting patients on mobile phones.

The registration forms along with the health facility monitoring forms (from each health facility) and the forms cross-checked on phones by the research assistant are then sent back to the research coordinator at the head office on weekly basis. The research coordinator then picks up 2 forms validated by the research assistant per health facility for further crosschecking. Apart from these measures, the research coordinator made monthly random spot checks at the health facility to observe the registration process.

Follow-up of clients:

During this phase, our main activity included completion of the pilot phase of the trial. Each of 150 patients (25 from each of 6 health centres) was followed up at six months post intervention and asked about quit status and validated with CO test.

Analysis of pilot findings

The quit rates at month 1 (Point Abstinence) and at month 6 (Continuous Abstinence) are given in the table 2 below. Overall, the quit rate for the Intervention Arm 1 and Intervention Arm 2 were higher as compared to the control arm at both month 1 and month 6.

Table 2: Results of the pilot trial

Intervention	Point abstinence at 1 month			Continuous abstinence at 6 months		
	No.	%	P-value	No.	%	P-value
Control	19/50	38	0.001	18/50	36	0.001
Intervention Arm 1 (behavioural support + bupropion)	37/50	74		37/50	74	
Intervention Arm 2 (behavioural support only)	44/50	88		37/50	74	

End pilot evaluation and revision of research and communication tools

In order to check the appropriateness of the intervention tools we conducted in-depth interviews with the following participants:

- 6 interviews with the patients (2 from Control Arm +4 from Intervention Arm 1 & 2)
- 2 interviews with Doctors (1 from Control arm + 1 from the Intervention Arm1)
- 2 interviews with DOTS Facilitator (1 from Control arm + 1 from the Intervention Arm 1)
- 1 interview with Field Supervisor
- 1 interview with District Tobacco Focal person

For the in-depth interviews we developed a semi-structured interview guide and enquired about the appropriateness of the messages, their form, cultural acceptability, timing in delivery, and other practicalities in understanding and delivering the tools. We also identified the areas of improvements and the suggestions/additions in the existing tools in the light of this qualitative enquiry.

- Generally there was a support for the correctness and appropriateness of the materials and process of trial. There had been some suggestions which are outlined below:
- The sketches and the messages of the flipbook were culturally, socially and religiously acceptable and there was nothing objectionable.
- There was a suggestion of addition of few pictures of the women smoking hookah in the introductory slides and also some in the first section of the flip-book.
- The patients and the health care staff opinioned that the messages and flipbook are clear and easy to understand. There was individual variation amongst the patient, with literacy as one of the important factor in ease of understanding. Nevertheless the support from the DOTS Facilitator seems to easily handle the situation, and further support the understanding of messages by the patients.
- Participants were very much satisfied about the coherence of the text and sketches and thought that the messages were effectively communicated by correlating both.
- It was suggested that Flip book (glossary images book) was very good tool for the counselling, but it needed size adjustment particularly increase in the width & size of the pictures.
- Factors as work load of the DOTS facilitator, literacy, age and gender of the patient did affect the time taken for counselling. Generally the time given for the counselling was found adequate.
- Counselling from the Flip books by the DOTS Facilitator was found to have good affect on patients, but the patients identified that some of the triggers do affect them even after quitting. They also suggested some form of moral boosting like small prizes.
- Visiting the health facility was a difficult aspect, as patients find it difficult to come on time because of factors as “distance from the health facility”, “business in the work and occupation”, and “non-affordability to come to hospital”. In this regards few of the suggestion to help patients remember and motivate to come to the health facilities are reminder from the health staff, and motivation of the patient in the form of some “gift/incentive” for encouragement.

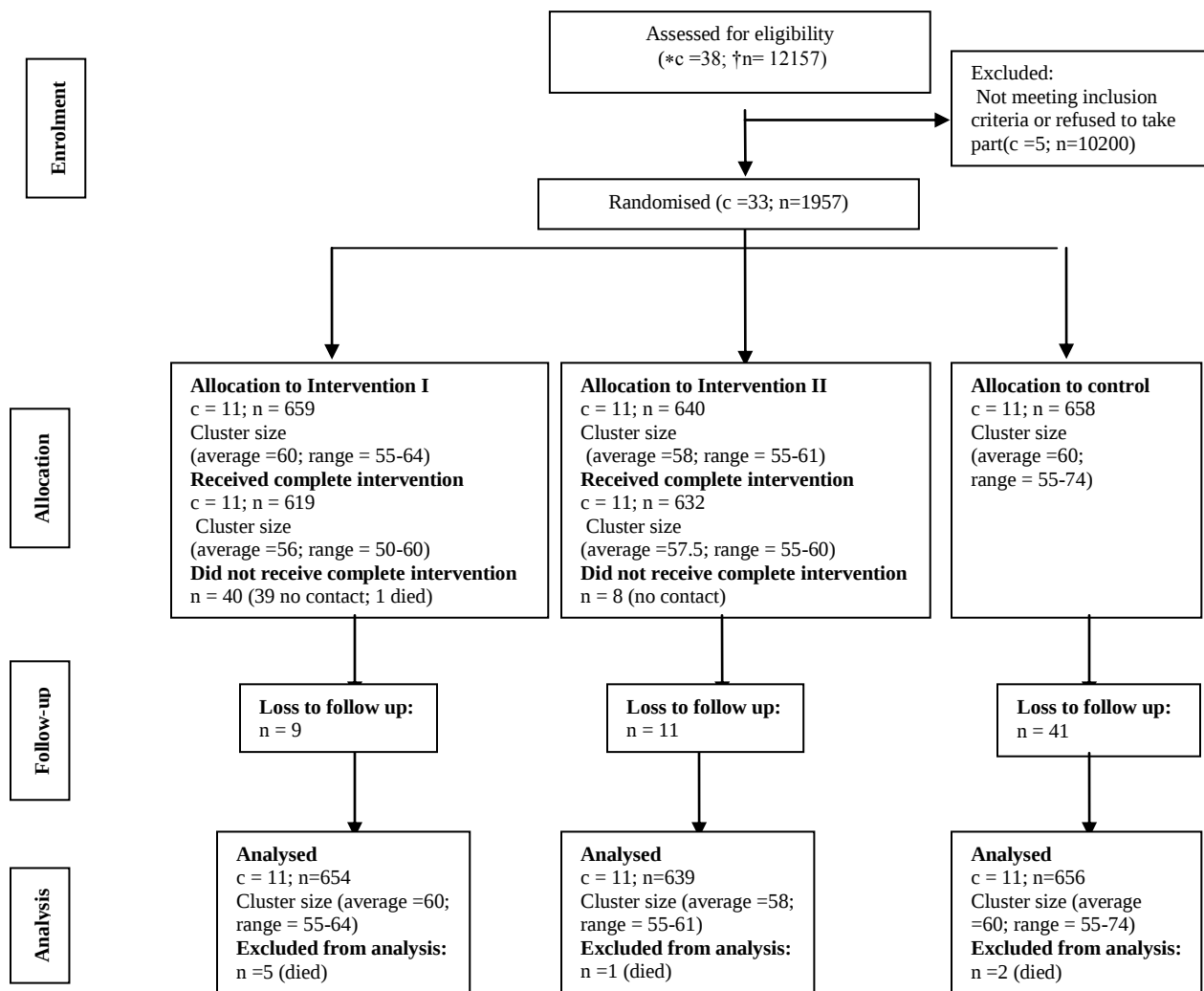
Based on these recommendations we revised our materials. We increased the sizes of the pictures and messages of the Flip book. We also included more pictures of the women and pictures showing rural cultural details. As suggested by audience pictures of the Hubble

Bubbles (Hookah in local language) have been added to the Flipbook/materials. We have also made the necessary changes in translation of training manual as suggested by the qualitative research.

6.3. Objective 3

6.3.1. Participant flow

We enrolled 1957 patients in 33 health centres (Figure 2). Eight participants died in total, five in arm I, one in arm II and two in the control arm and were excluded from the analyses. The remainder were included, giving 1949 participants in total (654, 639 and 656 participants in arm I, arm II and control arm respectively). Of these, 47 did not receive the complete intervention. Nine participants in arm I, 11 in arm II, and 41 in control arm were lost to follow-up.



* Cluster, † Individual

Figure 2: Progress of clusters and individuals through the phases of the trial

6.3.2. Baseline data

The three arms were well balanced with respect to the baseline characteristics (Table 3), although mean age, gender and smoking form showed slight differences across the groups.

Table 3: Baseline information for each group

CHARACTERISTICS	Intervention Arm I (Behavioural support + bupropion)	Intervention Arm II (Behavioural support only)	Control
CLUSTERS			
Number	11	11	11
Number of DOTS facilitators	11	11	11
Number of DOTS facilitators who were regular smokers	0	1	0
Male DOTS facilitators	9	9	8
THQ health centres - urban	3	2	2
PARTICIPANTS			
Number	659	640	658
Mean age (SD) in years	38.3 (12.4)	42.8 (13.5)	41.7 (13.4)
Number (%) of males	619/649 (95)	598/635 (94)	634/657 (97)
Mean age (SD) in years when started smoking	20.2 (6.9)	20.5 (6.4)	20.7 (7.2)
Mean duration (SD) in years of smoking	18.2 (11.4)	22.3 (13.2)	21.0 (12.3)
Median number (IQR) of cigarettes smoked per day	20 (12.0)	15 (10.0)	15 (10.0)
Median number (IQR) of cigarettes & hookah smoked per day	20 (13.0)	20 (15.0)	15 (10.0)
Numbers (%) in different age groups by years			
18-29	169/657 (26)	103/640 (16)	133/658 (20)
30-39	180/657 (27)	134/640 (21)	146/658 (22)
40-49	182/657 (28)	207/640 (32)	176/658 (27)
50-59	82/657 (12)	99/640 (15)	106/658 (16)
>= 60	44/657 (7)	97/640 (15)	97/658 (15)
Type of smoking			
Number (%) of cigarette smokers (whether or not also using hookah)	632/659 (96)	521/640 (81)	587/658 (89)
Number (%) of hookah-only smokers	27/659 (4)	119/640 (19)	71/658 (11)
Numbers (%) in different household income categories (based on monthly household income in US dollars)			
<= 37.5 (below poverty line)	62/649 (10)	67/634 (11)	98/649 (15)
37.6 – 80	179/649 (28)	205/634 (32)	243/649 (37)
81 – 115	147/649 (23)	117/634 (19)	127/649 (20)
>= 116	261/649 (40)	245/634 (39)	181/649 (28)

6.3.3. Outcomes

Behavioural support either alone or in combination with bupropion was significantly more effective in achieving continuous smoking abstinence at six months than usual care (OR 15.4, 95% CI:5.2-45.2 and OR 16.3, 95% CI:5.6-47.8 respectively) (table 4). Behavioural support

with bupropion was not significantly different in achieving continuous abstinence than behavioural support alone. The ICC was 0.28 suggesting a higher cluster effect than our initial assumption. Adjustment for all potential confounders (age; smoking duration; number of cigarettes and hookah smoked per day) gave ORs compared to control of 22.8 (95% CI:7.3-71.4) for intervention I, and 20.6 (95% CI:6.5-64.5) for intervention II (Table 3).

Table 4: Primary and secondary outcomes (intention to treat analysis)

Trial Arm	*N Abstinent (%)	Odds ratio (95% CI)	p-value	ICC
Primary outcome: **Continuous abstinence at 6 months				
†Arm I	275/654 (42.1)	16.3 (5.6-47.8)	<.0001	0.28
‡Arm II	254/639 (39.8)	15.4 (5.2-45.2)	<.0001	
Control	52/656 (7.9)	1	-	
Model 1: **Adjusted for age				
Arm I		15.9 (5.3-47.4)	<.0001	0.29
Arm II		15.9 (5.3-47.6)	<.0001	
Control		1	-	
Model 2: **Adjusted for smoking duration				
Arm I		15.9(5.3-47.7)	<.0001	0.29
Arm II		16.2(5.4-48.7)	<.0001	
Control			-	
Model 3: **Adjusted for number of cigarettes + hookah smoked per day				
Arm I		23.3 (7.6-71.8)	<.0001	0.29
Arm II		19.9 (6.5-61.2)	<.0001	
Control		1	-	
Model 4: **Adjusted for age & smoking duration				
Arm I		16.0 (5.3-47.9)	<.0001	0.29
Arm II		16.2 (5.4-48.6)	<.0001	
Control		1	-	
Model 5: **Adjusted for age & smoking duration & number of cigarettes + hookah smoked per day				
Arm I		22.8 (7.3-71.4)	<.0001	0.30
Arm II		20.6 (6.5-64.5)	<.0001	
Control		1	-	
Secondary outcomes				
Point abstinence (1 month): **Adjusted for age, smoking duration & number of cigarettes + hookah smoked per day				
Arm I	319/654 (48.8)	28.6 (8.5-96.3)	<.0001	0.34
Arm II	360/639 (56.3)	42.4 (12.6-143.2)	<.0001	
Control	59/656 (9.0)	1	-	
Point abstinence (6 month): **Adjusted for age, smoking duration & number of cigarettes + hookah smoked per day				
Arm I	395/654 (60.4)	14.8 (3.9-56.1)	<.0001	0.41
Arm II	318/639 (49.8)	9.5 (2.5-36.1)	.0010	
Control	142/656 (21.7)	1	-	
* Data are number abstinent/total number in arm (%) † Arm I: Behavioural support + bupropion ‡ Arm II: behavioural support only **Calculated using mixed-effects (multi-level) logistic regression Note: All analyses are adjusted for clustering; number and percentage of abstinent individuals in each group, estimated effect size (OR) and precision (95% CI), and coefficient of intra-class correlation (ICC) are presented.				

Secondary outcomes were the CO-validated point abstinence at one month and at six months. For point abstinence at one month, the OR for intervention I was 28.6 (95% CI:8.5-96.3) and for

intervention II 42.4 (95% CI:12.6-143.2), showing a greater effect of behavioural support alone on smoking abstinence. For point abstinence at six months, the corresponding ORs were 14.8 (95% CI:3.9-56.1) and 9.5 (95% CI:2.5-36.1), showing a greater effect of bupropion plus behavioural support on smoking abstinence. 112 trial participants were later on diagnosed to have TB, out of which 103 successfully completed their TB treatment. The complete case analysis for all outcomes (Table 5) concurred with the findings presented in the intention-to-treat analysis.

Table 5: Primary and Secondary Outcomes (complete case analysis)

Trial Arm	*N Abstinent (%)	Odds ratio (95% CI)	p-value	ICC
Primary outcome: Continuous abstinence at six months, **Adjusted for age & smoking duration & number of cigarettes + hookah smoked per day;				
†Arm I	275/606 (45.4)	25.1 (8.1-82.1)	<.0001	0.31
‡Arm II	254/620 (41.0)	20.6 (6.5-65.6)	<.0001	
Control	52/615 (8.5)	1	-	
Secondary outcomes, **Adjusted for age, smoking duration & number of cigarettes + hookah smoked per day				
Point abstinence (1 month)				
Arm I	319/611 (52.2)	35.6 (10.1-126.0)	<.0001	0.36
Arm II	360/621 (58.0)	45.7 (12.9-161.6)	<.0001	
Control	59/630 (9.4)	1	-	
Point abstinence (six month)				
Arm I	395/608 (64.9)	19.3 (4.8-77.6)	<.0001	0.43
Arm II	318/623 (51.0)	9.7 (2.4-38.7)	.0013	
Control	142/626 (22.7)	1	-	
* Data are n abstinent/total n in arm (%) † Arm I: Behavioural support + bupropion ‡ Arm II: Behavioural support only **Calculated using mixed-effects (multi-level) logistic regression				

Out of the 1949 TB suspects recruited in the trial, 107 were later diagnosed with TB disease (excluding eight who died). When the smoking cessation outcomes were assessed for this subgroup (with TB disease) in comparison to those who did not have TB disease, the odds of continuous abstinence at 6 months were found to be three times higher among TB patients (Table 6).

Table 6: Declared TB vs. Non TB disease group

TB Disease status	*N Abstinent (%)	Odds ratio (95% CI)	p-value
Continuous abstinence at six months			
Declared TB	57/107 (53.3)	2.87 (1.94- 4.25)	<0.0001
Declared Non-TB	524/1842 (28.5)	1	-
Point abstinence (1 month)			
Declared TB	61/107 (57.0)	2.28 (1.54- 3.38)	<0.0001
Declared Non-TB	677/1842 (36.8)	1	-
Point abstinence (six month)			
Declared TB	76/107 (71.0)	3.35 (2.18- 5.13)	<0.0001
Declared Non-TB	779/1842 (42.3)	1	-
* Data are number abstinent/total number in group (%)			

Of the individuals in intervention arm I using bupropion, 588 reported completing the full course and 214 reported adverse events secondary to therapy, mainly minor in nature (Table 7).

Table 7: Use of bupropion and occurrence of adverse events (in Arm I participants)

Intervention arm I (Bupropion + behavioural support)		No.
(5a) Bupropion use		
Did not use bupropion	Did not receive complete intervention	38
	Died	5
	Refused to take medicine	8
* Used bupropion	Regular use (7-weeks)	588
	Irregular use	20
Total		659
(5b) †Adverse events secondary to bupropion use		
Minor	Nausea	50
	Vomiting	23
	Headache	130
	Constipation	79
	Dry mouth	42
	Insomnia	28
	Other	5
Major	Tremor	1
	Seizure	0
	Allergic skin reactions	3
	Tinnitus	2
	Feeling 'spaced out'	1
	Confusion	0
	Elevated blood pressure	1
	Visual Disturbance	0
	Reduced Appetite	3
Total		368
* (Includes 1 participant who did not receive complete intervention – but returned for followed-up and reported use of bupropion)		
† Adverse events secondary to therapy were reported by 214 participants out of those 608 who took bupropion		

The approximate ICER for intervention I was \$91.51 and intervention II was \$9.13 per smoking abstinence, showing behavioural support alone to be substantially more cost-effective than the behavioural support and bupropion intervention (Table 8).

Table 8: Incremental cost-effectiveness ratio (ICER): based on the health care cost of delivering intervention

Trial Arm	Control	Arm I	Arm II
Smoking abstinence (%)	7.90	42.10	39.80
*Intervention delivery cost (\$)	0.57	20.87	2.57
^d Incremental intervention effect- IE (%)	-	34.20	31.90
^b Incremental cost- IC (\$)	-	20.30	2.00
[†] ICER (ages 35-54 years)(\$)	-	‡ 75.44	‡ 7.52
ICER (ages < 35 years)(\$)	-	110.14	10.98
ICER (ages > 54 years) (\$)	-	102.6	10.23
ICER (all age groups combined) (\$)	-	91.51	9.13
* includes health facility operational cost & smoking cessation material cost (brochures and/or drugs)			
^d Absolute difference b/w cessation percentages			
^b Average additional cost per smoker intervention delivered			
[†] Incremental cost-effectiveness ratio			
[‡] To obtain ICER for IC of 20 (ICER value for 10*2) and IC of 2 (ICER value for 1*2).			

The effect size we found for behavioural support was much larger than corresponding effect sizes in high-income countries. However, in Pakistan, where public awareness of the harms of smoking is limited, it is perhaps not surprising to observe a change of this magnitude for such interventions. An impact of this size is consistent with the major shifts observed in smoking behaviour in high-income countries in the 1970s; and is compatible with the S-shaped behaviour change curve, according to which a steep change occurs in the early phase of an intervention due to early adopters.

In this trial, the supplement of bupropion to behavioural support did not result in any significant additional benefit. The very few studies that made similar comparisons (none of which were in LMICs) did not show any additional benefit of a combination of bupropion and behavioural support over either one of these interventions.

6.3.4. Limitations – methods and intervention

We observed a difference in the ‘smoking form’ baseline variable across the three arms, with 19% hookah smoking seen in arm II compared to only 3 % in arm I. In Pakistan, hookah smoking is more common in rural settings. By adapting a simple stratified randomisation procedure, we wanted to achieve balance of THQs and RHCs between different arms. Since we randomised seven THQs to three arms, it was clearly not possible to obtain precise balance. Moreover, two THQs in arm II had been recently upgraded from RHCs and their catchment population was still substantially rural. However, this potential imbalance is unlikely to have caused any bias, as cigarette smoking is the predominant form of tobacco use in all arms and other variables appear reasonably balanced.

We started recruiting patients before the floods in July 2010. However, a number of health centres were affected by the calamity and as a result vast numbers of these patients either died or relocated elsewhere. In the affected health centres, we restarted recruitment from the beginning once the floods receded.

A behavioural support intervention (30 minutes) is more time consuming than the brief intervention (5-10 minutes) generally advocated within non-specialist health services. It is possible that a less time-intensive intervention (such as brief advice) could be just as effective (and/or more cost-effective) in achieving the abstinence rates observed here, at least in certain groups of patients.

In Pakistan, smokeless forms of tobacco use (mainly chewing tobacco) are also common and a prevalence of up to 17% has been reported in certain urban communities. We excluded patients who used only smokeless forms of tobacco mainly due to absence of any evidence that links smokeless tobacco with TB. It is possible that some patients who quit smoking may have taken up smokeless tobacco as an alternative. However, this is likely to be a rare occurrence as chewing tobacco is less commonly used in rural areas than in major cities. An Indian study observed no increase in the use of chewing tobacco in TB patients during the six months of treatment despite a high smoking quit rate.

We recruited patients suspected to have TB rather than just confirmed TB cases. This limited our ability to assess the effect of smoking cessation on TB outcomes. However, our decision to include this broader group was a pragmatic one. In health centres in Pakistan, there are generally ten times more patients suspected of TB than with confirmed TB. It would have been a missed opportunity not to offer smoking cessation to this group of patients and capitalise on the ‘teachable moment’ that this presentation offers.

We are mindful that continuous abstinence at twelve months would have given a closer approximation to lifelong abstinence. However, we followed Society for Research on Nicotine and Tobacco recommendations, which state that continuous abstinence should be measured for at least six months as it provides a reasonable balance between the need for validation and efficiency. There is some evidence that 40% of people diagnosed with TB who then stop smoking start again by six months post-treatment. However, the vast majority of our patients were only suspected of TB. Based on studies with a longer follow-up, we could expect, at the most, a 25% relapse at eighteen months.

6.4. Objective 4

Data collection tools: Following data collection guides have been developed after derivation of themes based on quantitative trial results and the themes emerging from the earlier qualitative study conducted in Phase II;

1. FGDs Guidelines for Trial Participants
2. Qualitative Interview schedule for Care Providers and Managers

Focus group discussions: Six in total - One FGD at each selected health facility with groups of 6–8 trial participants representing quitters/non-quitters of different age groups. Two FGDs have been conducted in Jhang district. FGDs in Sarghoda district will be conducted by April 20.

Semi-structured Interviews:

Following interviews have been planned and will be conducted by April 20.

Doctors – one at each selected health facility, total 6

DOTS facilitators– one at each selected health facility, total 6

7. Project Outputs

These are as follows:

7.1. Objective 1

We published a review on the relationship between TB and tobacco, which provided the basis for this study. Tropical Medicine and International Health published this paper in 2009 (output 1). We published the findings of the phase 1 in a peer-reviewed journal (output 2). An abstract of the study proposal was published in a Leeds Institute of Health Sciences, University of Leeds

newsletter. An introductory webpage was created on University of Leeds website. A summary of the study protocol was also published on the Current Controlled Trials website.

Output 1. Siddiqi K, Lee A. An integrated approach to treat tobacco addiction in countries with high tuberculosis incidence. *Trop Med Int Health*. 2009. April; 14(4):420-8

Output 2. Lee A, Siddiqi K, Khan A. Local determinants of tobacco use in Pakistan and the importance of context. *Journal of Smoking Cessation*. Nov 2010. 5(2), 151–156

7.2. Objective 2

We also published the study protocol in BMC public health (output 3).

Output 3. Siddiqi K, Khan A, Ahmad M, Shafiq-ur-Rehman. An intervention to stop smoking among patients suspected of TB - evaluation of an integrated approach BMC PUBLIC HEALTH 10 Art. No. 160 25 Mar 2010

We also submitted the results of the pilot study to the Lung Health Conference of the Union and presented our interim results in Berlin in a poster presentation in 2010.

In September 2010, we were invited to speak at a conference on TB and Tobacco in San Diego, CA. This was prompted by the publication of our study protocol in BMC Public Health earlier. In addition to the leading academics in this area, conference was attended by relevant people in the Union, WHO, NIH, CDC and other agencies. Our work in Pakistan was greatly appreciated and considered as cutting edge. In fact we were acknowledged as the only group who are conducting an RCT in this area. There were several useful suggestions and interest from all parties. The outcome was formalisation of this consortium as a TB and Tobacco consortium which we are now a part. The conference helped us to get our work noticed by the interested academic and policy community. It gave us lots of ideas for improving our work and further research. It also helped us to establish collaboration with others.

7.3. Objective 3

We have submitted a paper (output 4) summarising the main findings of our trial to the Lancet which is currently under review. We are also preparing two more manuscripts (output 5 & 6) based on the sub-analysis of the trial data sets.

Output 4. Siddiqi K, Khan A, Ahmad M, Dogar O, Kannan M, Newell J, Thomson, H. Action to Stop Smoking In Suspected Tuberculosis (ASSIST) in Pakistan: a cluster-randomised trial. *The Lancet*. 2012 (submitted).

Output 5. Dogar O, Siddiqi K, Newell J. Do Hookah smokers quit after receiving behavioural support in Pakistan: a pilot RCT (being prepared).

Output 6. Dogar O, Siddiqi K, Newell J. What are the key determinants of smoking cessation among TB suspects? Sub-analysis of ASSIST Pakistan trial (being prepared).

7.4. Objective 4

We are also preparing a manuscript (output 7) summarising the findings from the qualitative study in this phase of the study (being prepared).

Output 7. Siddiqi K, Dogar O, Khan A, Ahmad M. What are the barriers and constraints in getting people to stop smoking with TB DOTS? A qualitative investigation.

At the 41st Union World Conference on Lung Health (11- 15 November, 2010) we proposed a post-graduate course session on ‘Tobacco cessation and TB: research to implementation of intervention’. The session was accepted for presentations in the 42nd Union World Conference on Lung Health (26-30 October, 2011). This session will be attended by interested policy makers, managers and clinicians around the world and will be an opportunity for us to share our work with them.

A session on this study has also been presented as part of one of the scientific symposia in the 15th World Conference on Tobacco or Health held in March 2012 in Singapore.

8. Project Outcomes

These are as follows:

8.1. Objective 1

During our activities in phase I of this research, we were successful in gathering support from both TB and Tobacco control programmes in Pakistan. Meetings with policy makers and FGD with potential users and clients highlighted the need to develop smoking cessation and provided support to our idea to embed this within the existing programme. The results encouraged us to expect this study to have a substantial impact in Pakistan. We also expected this to have international repercussions, as there are several countries like Pakistan who are struggling with the dual epidemic of TB and Tobacco.

8.2. Objective 2

During this phase, the Tobacco control programme of Pakistan invited us to lead the development of national strategic plan for tobacco control along with WHO Pakistan. The strategic plan was based on the new MPOWER package on tobacco control. In Pakistan, we were also in close communication with the national TB programme. There is now an acknowledgement that the smoking cessation intervention can be a component of TB programme activities. Once we conclude on the effectiveness and cost-effectiveness of the smoking cessation intervention, our embedded approach within the TB programme would lead to a high impact in future.

At the 41st Union World Conference on Lung Health (11- 15 November, 2010) we proposed a post-graduate course session on ‘Tobacco cessation and TB: research to implementation of intervention’. The session was accepted for presentations in the 42nd Union World Conference on Lung Health (26-30 October, 2011). This session was attended by interested policy makers, managers and clinicians around the world and was an excellent opportunity for us to share our work with them.

8.3. Objective 3

A session on this study has also been proposed as part of one of the scientific symposia in the 15th World Conference on Tobacco or Health to be held in March 2012 in Singapore.

8.4. Objective 4

Smoking cessation intervention has already been included in the strategic plans of the provincial TB control programmes in Pakistan and programme managers are keen to scale up. As part of phase IV of the study and remaining within our allocated resources for the trial, we supported the national programme in scaling up smoking cessation intervention in 10 - 20 districts in Punjab province. Implementing intervention in these districts provided provincial TB programme the early experience of scaling up which is helpful to the programme in doing a full provincial scale up later on. The scale up in 10 - 20 district involved training approximately 300 - 600 doctors and DOTS facilitators in smoking cessation interventions and potentially benefit 30,000 to 35,000 (or 15,000 - 17,500 as a conservative estimate) smokers TB patients coming in contact with these professionals every year. Extrapolating from our trial results and using a conservative estimate, there is a possibility of getting approximately 10,000 (5,000) smokers to quit per year.

9. Overall Assessment and Recommendations

This trial revealed that providing behavioural support in primary health care settings in Pakistan is highly effective and cost-effective in getting smokers who are suspected of TB to give up smoking and stay abstinent for at least six months. Our research makes a strong argument to integrate behavioural support within TB DOTS programme in order to offer smoking cessation support to a large cohort of patients who come in contact with the programme. This is a very cost-effective intervention to prevent morbidity and mortality from several tobacco-related non-communicable diseases. In future research, we also need to demonstrate that smoking cessation improves outcomes for TB patients too. We would recommend donor agencies to prioritise funding smoking cessation interventions in low- and middle-income countries where TB and tobacco is highly prevalent. We would also recommend agencies interested in tobacco research to support studies investigating links between smoking cessation and improved TB outcomes. We believe that our research has so far shown that tobacco control can be achieved within TB programmes now we need to show that tobacco control also achieves TB control.

10. Appendix - Research outputs

Output 1

*Title: An integrated approach to treat tobacco addiction in countries with high tuberculosis incidence

Subtitle:

*By: Full Name(s) of Author(s): Kamran Siddiqi, Andrew Lee

Report Type: Research paper.

*Date: April, 2009

Published by: Full Name of Publisher: Tropical Medicine & International Health, Blackwell Publishing Ltd

Location: Series Name: 14(4)

Number of Series part: 420-8

*IDRC Project Number: 104825-002

*IDRC Project Title: An intervention to stop tobacco use among patients suspected of TB – evaluation of an integrated approach

*Country/Region: Country(ies) or region(s) where project was carried out: Pakistan

*Full Name of Research Institution: University of Leeds and Association of Social Development

*Address of Research Institution: 101, Charles Thackrah building, University of Leeds, Leeds, UK and Association of Social Development, House No. 12, Street 48, Sector F - 7/4, Islamabad, Islamabad, Pakistan.

*Name(s) of Researcher/Members of Research Team: Kamran Siddiqi

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*This report is presented as received from project recipient(s). It has not been subjected to peer review or other review processes.

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*Abstract: Research outputs should include an abstract of 150-200 words specifying the issue under investigation, the methodology, major findings, and overall impact.

Communicable diseases as well as maternal and child health in low- and middle-income countries continue to be the main focus of global attention. There are also rising trends in the prevalence of non-communicable diseases and further increases are predicted. Several countries are facing this 'dual burden of disease'. There is therefore a need to find ways to integrate the prevention and

control of non-communicable diseases into the current health agenda. Tobacco treatment interventions in patients suspected with tuberculosis (TB) offer one such opportunity for a linked healthcare response. Many countries with a high incidence of TB are doubly burdened by an epidemic of tobacco use and tobacco-related diseases. Tobacco use increases the risk of TB infection and is associated with poor treatment compliance, increases in relapse rates and higher secondary mortality. In countries where TB is epidemic, this modest relative risk of infection leads to a significant attributable risk. Regular clinical contact with patients suspected with TB during the diagnosis and treatment phases provides considerable opportunity for health promotion to influence their tobacco-related behaviour. Consequently, treating tobacco addiction in patients suspected with TB is likely to improve the control of TB and prevent tobacco-related diseases. However, despite a high prevalence of tobacco use among TB patients, the treatment of tobacco addiction has not been a priority of TB control programmes. In countries with the dual epidemics of TB and tobacco use, considerable health and economic gains could potentially be made. If effective, such an approach would be highly desirable. We argue that further research assessing the cost-effectiveness and feasibility of linking healthcare interventions such as the treatment of tobacco addiction among TB suspects should receive high priority.

*Keywords: Include up to six subject keywords separated by commas.
tobacco use cessation, tuberculosis

Output 2

*Title: An intervention to stop smoking among patients suspected of TB - evaluation of an integrated approach

Subtitle:

*By: Full Name(s) of Author(s): Kamran Siddiqi, Amir Khan, Maqsood Ahmad, Shafiq-ur-Rehman

Report Type: Research paper.

*Date: October, 2010

Published by: Full Name of Publisher: BMC Public Health, BioMed Central

Location: Series Name: 10

Number of Series part: 107

*IDRC Project Number: 104825-002

*IDRC Project Title: An intervention to stop tobacco use among patients suspected of TB – evaluation of an integrated approach

*Country/Region: Country(ies) or region(s) where project was carried out: Pakistan

*Full Name of Research Institution: University of Leeds and Association of Social Development

*Address of Research Institution: 101, Charles Thackrah building, University of Leeds, Leeds, UK and Association of Social Development, House No. 12, Street 48, Sector F - 7/4, Islamabad, Islamabad, Pakistan.

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*Abstract: Research outputs should include an abstract of 150-200 words specifying the issue under investigation, the methodology, major findings, and overall impact.

Background: In many low- and middle-income countries, where tobacco use is common, tuberculosis is also a major problem. Tobacco use increases the risk of developing tuberculosis, secondary mortality, poor treatment compliance and relapses. In countries with TB epidemic, even a modest relative risk leads to a significant attributable risk. Treating tobacco dependence, therefore, is likely to have benefits for controlling tuberculosis in addition to reducing the non-communicable disease burden associated with smoking. In poorly resourced health systems which face a dual burden of disease secondary to tuberculosis and tobacco, an integrated approach to tackle tobacco dependence in TB control could be economically desirable. During TB screening, health professionals come across large numbers of patients with respiratory symptoms, a significant proportion of which are likely to be tobacco users. These clinical encounters, considered to be “teachable moments”, provide a window of opportunity to offer treatment for tobacco dependence.

Methods/Design: We aim to develop and trial a complex intervention to reduce tobacco dependence among TB suspects based on the WHO ‘five steps to quit’ model. This model relies on assessing personal motivation to quit tobacco use and uses it as the basis for assessing suitability for the different therapeutic options for tobacco dependence.

We will use the Medical Research Council framework approach for evaluating complex interventions to: (a) design an evidence-based treatment package (likely to consist of training materials for health professionals and education tools for patients); (b) pilot the package to determine the delivery modalities in TB programme (c) assess the incremental cost-effectiveness of the package compared to usual care using a cluster RCT design; (d) to determine barriers and drivers to the provision of treatment of tobacco dependence within TB programmes; and (e) support long term implementation. The main outcomes to assess the effectiveness would be point abstinence at 4 weeks and continuous abstinence up to 6 months.

Discussion: This work will be carried out in Pakistan and is expected to have relevance for other low and middle income countries with high tobacco use and TB incidence. This will enhance our knowledge of the cost-effectiveness of treating tobacco dependence in patients suspected of TB.

*Keywords: Include up to six subject keywords separated by commas.

Tobacco use cessation, tuberculosis

Output 3

*Title: Local Determinants of Tobacco Use in Pakistan and the Importance of Context

Subtitle:

*By: Full Name(s) of Author(s): Andrew Lee, Kamran Siddiqi, Muhammad Amir Khan, Maqsood Ahmed, Shafiq-Ur-Rehman, Nazia Shams and Athar Nazir

Report Type: Research paper.

*Date: May 2010

Published by: Full Name of Publisher: Australian Academic Press

Location: Series Name:

Number of Series part:

*IDRC Project Number: 104825-002

*IDRC Project Title: An intervention to stop tobacco use among patients suspected of TB – evaluation of an integrated approach

*Country/Region: Country(ies) or region(s) where project was carried out: Pakistan

*Full Name of Research Institution: University of Leeds and Association of Social Development

*Address of Research Institution: 101, Charles Thackrah building, University of Leeds, Leeds, UK and Association of Social Development, House No. 12, Street 48, Sector F - 7/4, Islamabad, Islamabad, Pakistan.

*Name(s) of Researcher/Members of Research Team: Kamran Siddiqi

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*Abstract: Research outputs should include an abstract of 150-200 words specifying the issue under investigation, the methodology, major findings, and overall impact.

Introduction: The tobacco epidemic is surging in developing countries. While the determinants of tobacco use are well known, it is less certain whether they are similar in developed and developing countries. This has important ramifications for the implementation of interventions locally. This qualitative study explored the determinants and importance of context on tobacco use in Pakistan. Methods:

Focus group discussions were conducted in two districts with doctors, nurses and patients from local tuberculosis clinics. Results: Peer influence, social acceptability, affordability and visibility of tobacco, public understanding and personal perception of risks influence tobacco use. Individual factors, such as personal curiosity, adversity and stress, also affected tobacco uptake and use. Patients were willing to pay for effective cessation treatment provided the costs were comparable to their expenditure on tobacco. Discussion: Factors such as peer and social influences are similar to those reported elsewhere. However, local variations exist in the degree of sociocultural acceptability, visibility of tobacco use, public understanding of risks and individual situational factors that influence tobacco use. Patients are prepared to pay for treatment, but there are gender differences in what can be afforded. For tobacco cessation interventions to be effective, local adaptations are essential to ensure cultural- and contextual-appropriateness.

*Keywords: Include up to six subject keywords separated by commas.

tobacco use, smoking, cessation, focus groups, tuberculosis