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# Smoking cessation interventions for pulmonary tuberculosis treatment outcomes (Review)

Jeyashree K, Kathirvel S, Shewade HD, Kaur H, Goel S

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Smoking cessation interventions for pulmonary tuberculosis treatment outcomes.
*Cochrane Database of Systematic Reviews* 2016, Issue 1. Art. No.: CD011125.
DOI: 10.1002/14651858.CD011125.pub2.

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[Intervention Review]

# Smoking cessation interventions for pulmonary tuberculosis treatment outcomes

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**Editorial group:** Cochrane Tobacco Addiction Group.
**Publication status and date:** New, published in Issue 1, 2016.
**Review content assessed as up-to-date:** 29 July 2015.

**Citation:** Jeyashree K, Kathirvel S, Shewade HD, Kaur H, Goel S. Smoking cessation interventions for pulmonary tuberculosis treatment outcomes. *Cochrane Database of Systematic Reviews* 2016, Issue 1. Art. No.: CD011125. DOI: 10.1002/14651858.CD011125.pub2.



## ABSTRACT

### Background

Active smoking increases the risk of tuberculosis (TB) infection 2 to 2.5 times and is significantly associated with recurrent TB and TB mortality. Observational studies have shown associations between smoking and poor TB treatment outcomes such as increased loss to follow-up rate, severity of disease, drug resistance and slow smear conversion. Since most smoking-related immunologic abnormalities are reversible within six weeks of stopping smoking, smoking cessation may have substantial positive effects on TB treatment outcomes, TB relapse and future lung disease.

### Objectives

To analyse the effect of tobacco smoking cessation interventions (SCIs) on the treatment outcomes of people with adult pulmonary TB.

### Search methods

We searched the Cochrane Tobacco Addiction Group Specialised Register using free-text and MeSH terms for TB and antitubercular treatment. We also searched MEDLINE and EMBASE using the same topic-related terms, combined with the search terms used to identify trials of tobacco cessation interventions from the Specialised Register. We also searched reference list of articles and reviews, the Conference Paper Index, clinicaltrials.gov and grey literature. The searches are current to 29th July 2015.

### Selection criteria

Individual and cluster-randomised controlled trials (RCTs), regardless of date, language and publication status, studies of adults with pulmonary TB on first-line anti-tubercular drugs, with interventions at either an individual or a population level, delivered separately or as part of a larger tobacco control package. This included any type of behavioural or pharmaceutical intervention or both for smoking cessation.

**Data collection and analysis**

Using the eligibility criteria, two authors independently checked the abstracts of retrieved studies for relevance, and acquired full trial reports of candidates for inclusion. The authors resolved any disagreements on eligibility by mutual consent, or by recourse to a third author. Two authors intended to independently extract study data from eligible studies into a data extraction form and compare the findings, synthesise data using risk ratios, and assess risk of bias using standard Cochrane methodologies. However, we found no eligible trials.

**Main results**

There were no randomised controlled trials that met the eligibility criteria. A number of potentially eligible studies are underway, and we will assess them for inclusion in the next update of this review.

**Authors' conclusions**

There is a lack of high-quality evidence, i.e. RCTs, that tests the effectiveness of cessation interventions in improving TB treatment outcomes. There is a need for good-quality randomised controlled trials that assess the effect of SCIs on TB treatment outcomes in both the short and long term. Establishing such an evidence base would be an essential step towards the implementation of SCIs in TB control programmes worldwide.

## PLAIN LANGUAGE SUMMARY

**Can smoking cessation interventions among adults with pulmonary tuberculosis improve their tuberculosis treatment outcomes?**

**Review question**

Do treatments to help people with tuberculosis (TB) of the lungs to stop smoking also improve how they respond to treatment for their TB?

**Background**

Tuberculosis (TB) is a bacterial infection that can affect any organ of the human body. TB of the lungs can be transmitted from one person to another through the air when people who have TB cough, sneeze or spit. TB is a major cause of death in low- and middle-income countries. Smokers are twice as likely to become infected with TB as nonsmokers. Smoking is a common risk behaviour among people with TB. People who breathe in secondhand smoke are also more likely to be infected with TB. When people who smoke are infected with TB, they are more likely to have a more serious form of TB. They are also more likely to refuse or to stop their treatment and are less likely to respond to drug treatment.

Smoking can cause problems for the body's immune system (the system that protects a person from disease). However, research shows that most of these problems can be resolved after stopping smoking for six weeks. We therefore wanted to test whether quitting smoking can help people with TB by improving how they respond to treatment and reducing their infection levels.

**Review methods**

We searched various research databases that contain published and ongoing research on this topic up to the 29th of July 2015. We searched for studies written in any language, published and unpublished. We planned to include only studies that tested the success of a treatment to help someone with TB stop smoking, by comparing it to another treatment or to no treatment, using randomised controlled trials (RCTs). We considered treatments targeted at individuals (adults with TB and on TB treatment) or at whole populations. This included counselling or drug-based interventions for quitting smoking. We were interested in studies if they measured the number of people who completed the treatment for TB or the number of people cured of TB, or both.

**Key results**

We found no studies that met the eligibility criteria above. This is therefore an 'empty' review. However, there are studies that are currently being carried out, which may be reported in our next update of this review.

**Quality of the evidence**

There is as yet no high-quality evidence that can tell us whether treatments to help people with TB to stop smoking also help them to complete their TB treatment and to respond better to that treatment. There is therefore a need for good-quality research studies that test the usefulness of treatments to quit smoking in people with TB.

# BACKGROUND

The Global Adult Tobacco Survey (GATS India 2010), conducted between 2008 and 2010, has revealed that in the GATS countries 48.6% of men and 11.3% of women used some form of tobacco; of these, 40.7% of men and 5% of women were smokers. In men, smoking prevalence ranged from 21.6% in Brazil to 60.2% in Russia. In women, smoking ranged between 1.4% in Vietnam to 24.4% in Poland. Tobacco smoking in forms other than cigarettes, such as bidis, is common in India and Bangladesh.

The tuberculosis (TB) mortality rate has decreased by 45% and TB prevalence has decreased by 41% between 1990 and 2013, suggesting progress towards achieving the Millennium Development Goal (MDG) 2015 (GTR 2013; GTR 2014; MDG 2015). MDG Target 6C aims to halt the incidence and prevalence of TB, and mortality caused by it, and to begin to reverse its incidence by 2015. Globally, there were nine million new TB cases estimated in 2013 (GTR 2014). TB is the second leading cause of death by infectious diseases worldwide after HIV. In 2013, 1.1 million (range: 0.98 to 1.3 million) HIV-negative people died from TB and 0.36 million (range: 0.31 to 0.41 million) HIV-positive people died from TB (GTR 2014).

## Description of the condition

There is considerable information on the risks of TB infection, morbidity and mortality due to active and passive smoking in low- and middle-income countries. More than 20% of global TB incidence may be attributable to smoking (WHO 2009). A qualitative systematic review by the International Union Against Tuberculosis and Lung Diseases (The Union 2007) indicated that active or passive exposure to tobacco smoke is significantly associated with TB infection and disease (Den Boon 2005). Smoking increases the risk of TB disease by 2 to 2.5 times, and active smoking is significantly associated with recurrent TB and TB mortality (Bates 2007; Lin 2009; WHO Factsheet 2009). These effects appear to be independent of the effects of alcohol use, socioeconomic status and a large number of other potential confounders. Smoking was also found to increase the risk of extrapulmonary TB (Maurya 2002).

Studies suggest that people who smoke are less likely to adhere to antitubercular medication (Schneider 2007; Shea 1992). Lavigne 2006 suggests that men in particular are less adherent to TB treatment and that nonsmokers are almost twice as likely to adhere to their medication than smokers (odds ratio 1.8, 95% confidence interval (CI) 1.0 to 3.3), leaving them at a lower risk of loss to follow-up and persistent infectivity. Smoking has also been found to be associated with TB relapse, even after adjustment for socioeconomic variables (Batista 2008). Leung 2015 found that in their study population 16.7% of unsuccessful treatment outcomes were attributable to smoking. The key reason was loss to follow-up in current smokers and death in ex-smokers. A narrative review of the available literature from cohort, case-control and cross-sectional studies showed associations between smoking and TB treatment outcomes, such as loss to follow-up, slow sputum smear conversion, severity of disease and drug resistance (The Union 2008). People who smoke also place their families at risk of infection via household passive smoking (Patra 2015).

## Description of the intervention

Most smoking-related immunologic abnormalities are reversible within six weeks of smoking cessation (Schneider 2007). Smoking cessation may therefore have substantial positive effects on TB treatment outcomes, TB relapse, future lung disease (Lavigne 2006) and death (Lin 2007). Systematic reviews of randomised trials have identified a range of behavioural and pharmacotherapeutic interventions that aid smoking cessation. Effective behavioural interventions include brief advice from a physician (Stead 2013), face-to-face individual (Lancaster 2005) or group-based counselling (Stead 2005), and counselling and support delivered via telephones and mobile phone technology alone or in combination with pharmacotherapy (Stead 2012a; Stead 2012b). Effective pharmacotherapies include all forms of nicotine replacement therapy (NRT) (Stead 2013), the nicotine receptor partial agonists varenicline and cytisine (Cahill 2012), and the antidepressants bupropion and nortriptyline (Hughes 2014). Interventions for smoking cessation that have been shown to be effective in the general population can be expected to work in people with TB. This review focuses specifically on the effect of smoking cessation on TB outcomes, as opposed to the effects of smoking cessation interventions (SCIs) on subsequent cessation.

## How the intervention might work

Smoking and TB damage lungs and interact at an immunologic and cellular level to reduce antitubercular treatment efficacy (Schneider 2007). Smoking suppresses the innate and adaptive immune responses, with decreased levels of pro-inflammatory cytokines and circulatory immunoglobulins, which in turn reduce the activity of alveolar macrophages, dendritic cells and natural killer cells. Tobacco cessation improves ciliary function and local immunological responses, thereby improving cure rates in people with TB (Schneider 2007). As nonsmokers with TB are found to have better medication adherence rates (Balbay 2005; Lavigne 2006) cessation could be expected to reduce the loss to follow-up rate, improve recovery, shorten infectivity and prevent treatment failures. Different SCIs, such as cognitive behavioral therapy (CBT) and pharmacotherapies (e.g. nicotine replacement therapy) have different mechanisms of action. Pharmacotherapy may interact with TB drugs and reduce their effectiveness; however, this is not the case for behavioural therapies, such as CBT (Schneider 2007).

### Why it is important to do this review

The World Health Organization (WHO) has strongly recommended co-ordination between national TB and tobacco control programmes, and the registration of people with TB using tobacco, to enable counselling and provision of appropriate treatment (GTR 2011).The International Union against Tuberculosis and Lung Diseases recently called for the inclusion of brief smoking cessation advice in standard TB case management (Schneider 2007). The second phase of the WHO/The Union collaboration on tobacco and TB was to prepare a policy paper providing guidance to managers of national TB and tobacco control programmes, to enable them to plan and implement joint tobacco control activities through the healthcare system, within the framework of existing and evolving TB strategies (The Union 2007). There is therefore a need to establish a strong evidence base to inform the implementation of individual-level interventions for tobacco cessation to improve TB treatment outcomes.

## OBJECTIVES

To analyse the effect of tobacco smoking cessation interventions on the treatment outcomes of people with adult pulmonary TB.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Individual and cluster-randomised controlled trials (RCTs), regardless of date, language and publication status (published, unpublished, in press, in progress).

#### Types of participants

We planned to include studies of adult smokers (15 years and older), regardless of gender, with pulmonary TB, on Directly Observed (antitubercular) Treatment Short course (DOTS) or non-DOTS regimens with first-line antitubercular drugs. We planned to include trials recruiting both new and retreatment pulmonary TB patients. We exclude studies of people with only extrapulmonary TB. We planned to include studies comprising exclusively people with TB and also studies with a subgroup of those with TB provided with SCIs.

#### Types of interventions

Individual- and population-level SCIs, delivered separately or as part of a larger tobacco control package. This includes any type of behavioural or pharmaceutical intervention or both for smoking cessation. Behavioural interventions can include brief advice from a physician, dentist, nurse or pharmacist; face-to-face individual or group-based counselling, or counselling and support delivered via telephone and mobile phone technology. Pharmacotherapies can include all forms of NRT; the nicotine receptor partial agonists varenicline and cytisine; and the antidepressants bupropion and nortriptyline. Other types of interventions, such as hypnotherapy, acupuncture and exercise therapy alone or in combination for smoking cessation were also eligible. In the case of complex or multiple interventions, at least one intervention arm should contain the SCI only, without any intervention unrelated to tobacco control. The comparator arm may include no intervention, placebo, another SCI or an intervention unrelated to tobacco control, alone or in combination. Eligible interventions were to target first-hand rather than secondhand smoke exposure.

#### Types of outcome measures

##### Primary outcomes

• Cure rate: 'Cured' defined as "A pulmonary TB patient with bacteriologically-confirmed TB at the beginning of treatment who was smear- or culture-negative in last month of treatment and on at least one previous occasion" (WHO 2013);
• Treatment completion rate: 'Treatment completed' defined as "A TB patient who completed treatment without evidence of failure, but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable" (WHO 2013);
• Loss to follow-up rate: 'Loss to follow-up' defined as "A TB patient who did not start treatment or whose treatment was interrupted for two consecutive months or more" (WHO 2013);
• Treatment failed rate: 'Treatment failed' defined as "A TB patient whose sputum smear or culture is positive at month five or later during treatment" (WHO 2013);
• Mortality rate: 'Died' defined as "A TB patient who dies for any reason before starting or during the course of treatment" (WHO 2013);
• Not evaluated: 'Not evaluated' defined as "A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit" (WHO 2013).

##### Secondary outcomes

• Sputum smear conversion rates at the third month post-antitubercular therapy;
• Tobacco smoking quit rates: Smoking cessation rates (abstinence sustained over a period of time or abstinence at a given point in time); biochemically-verified rates or rates based on self-reported quitting.We assume that participants lost to follow-up are smoking;
• Adverse events or side effects.

## Search methods for identification of studies

### Electronic searches

We searched the Cochrane Tobacco Addiction Group Specialised Register (Cochrane Library 2015, Issue 7) using free-text and MeSH terms for TB and antitubercular treatment. We also searched Ovid MEDLINE (1946 to Week 30, 2015), PubMed (to Week 30, 2015) and EMBASE (1974 to Week 30, 2015) using the same topic-related terms, combined with the search terms used to identify trials of tobacco cessation interventions from the Specialised Register (See Appendix 1, Appendix 2, and Appendix 3).

### Searching other resources

We sought to identify abstracts of conferences on TB and any relevant journal articles that were not indexed by the electronic resources listed, using resources such as the Conference Paper Index. We checked reference lists of the included articles and any relevant reviews for studies that the primary search of electronic resources did not identify. A grey literature search included ISI Web of Science with conference proceedings, ClinicalTrials.gov, national and international trials registers, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch/), metaRegister of Controlled Trials (mRCT) (controlledtrials.com/mrct/) and trial results registers, theses and dissertations databases (1960 onwards), search engines such as Google Scholar, the Turning Research into Practice (TRIP) database, and guidelines and their reference lists as sources of studies (Appendix 3).

## Data collection and analysis

### Selection of studies

Two review authors independently checked the abstracts of retrieved studies for relevance, and acquired full trial reports of candidate studies for inclusion. The review authors resolved any disagreements by mutual consent, or by recourse to a third review author. We classified as excluded those studies for which we obtained full reports but which do not meet the inclusion criteria. We recorded the selection process in sufficient detail to enable us to complete a PRISMA flow diagram and a Characteristics of excluded studies table, giving reasons for the decisions to exclude.

### Data extraction and management

Two review authors planned to independently extract study data into a data extraction form and compare their findings. We resolved any disagreement by discussion with a third review author. Where available, we planned to record the following information in a Characteristics of included studies table:

1. Methods: design, study name (if applicable), recruitment period and procedures, country, number of study centres, setting.
2. Participants: N (intervention/control), definition of smoker used, specific demographic characteristics (e.g. mean age, age range, gender, ethnicity), mean cigarettes/bidi per day, mean Fagerström Test for Nicotine Dependence (FTND) score, inclusion criteria, and any relevant exclusion criteria.
3. Interventions: Description of intervention(s) (treatment, dosage, regimen, behavioural support), description of control (treatment, dosage, regimen, behavioural support); what comparisons will be constructed between which groups, any concomitant medications and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, time points reported, biochemical validation, definitions of abstinence, proportion of participants with follow-up data; data for intention-to-treat (ITT) and per protocol analyses.
5. Potential conflicts: trial funding, conflicts of interest of trial authors.

In the case of abstract-only and unpublished studies, we planned to contact the investigators or study sponsors to obtain full articles, key study characteristics, and missing numerical outcome data.

### Assessment of risk of bias in included studies

We planned to rate each included trial as being at high, low or unclear risk of bias for the following domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. We had planned to note in the 'Risk of bias' table the proportion of participants for whom the outcome was imputed, and whether there was either high or differential loss to follow-up between study groups. Where information on risk of bias related to unpublished data or correspondence with a trialist, we planned to note this in the table. We planned to summarise the 'Risk of bias' judgements across studies for each of the domains listed, and display the summary results in a 'Risk of bias' figure ('traffic lights' or bar chart, depending on the number of included studies). As cluster-randomised trials were also eligible for inclusion in our review, we planned to assess for biases specific

to such trials, including recruitment bias, baseline imbalance, loss of clusters, incorrect analysis, and comparability with individually randomised trials (Higgins 2011).

### Measures of treatment effect

All primary and secondary outcomes are dichotomous. Following the Cochrane Tobacco Addiction Group's recommended method of data analysis, we planned to use the risk ratio (RR) for summarising individual trial outcomes and for estimates of pooled effect, and present these with a 95% confidence intervals (CI).

### Unit of analysis issues

The unit of analysis planned was the individual smoker, unless the trial was cluster-randomised, in which case the relevant cluster (e.g. community, institution or caregiver) would be the unit of analysis. In the case of a cluster-randomised trial using the individual as the unit of analysis, we planned to report the trialists' methods for adjusting analyses for intraclass correlation. For cluster-RCTs, the plan was to present cluster-adjusted results, extract the 95% CI, and use the inverse variance method to combine trials.

### Dealing with missing data

We planned to contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where relevant (e.g. when a study was reported as abstract only). Where this was not possible, and the missing data were thought to introduce serious bias, we planned to explore the impact of including such studies in the overall assessment of results using a sensitivity analysis. Specifically, we planned to define any missing outcome data as failure (not cured) and conduct sensitivity analyses based on this assumption, and to explore the potential impact of these missing data in the Discussion section. We planned to treat participants who dropped out or who were lost to follow-up after randomisation as smoking, and to note any exceptions to this.

### Assessment of heterogeneity

We planned to evaluate levels of clinical heterogeneity (study characteristics, methods, outcomes) between included studies, to decide whether or not it was appropriate to pool study data. We also planned to use the $I^2$ statistic to assess the statistical heterogeneity between studies (Higgins 2011). This describes the percentage variability in effect estimates that is due to heterogeneity rather than to sampling error (chance). We would consider a value greater than 50% to indicate substantial heterogeneity.

### Assessment of reporting biases

We planned to address any suspected selective reporting of outcomes, as assessed by either of the review authors, by contacting the study authors for more information about the reported and unreported outcomes. We also planned to create a funnel plot to assist in identifying possible publication bias, methodological flaws, or small-study effects in the case of a sufficient number of included studies (10 or more) contributing to the outcome. We searched for studies which had been completed but for which results were unavailable.

### Data synthesis

We planned to conduct intention-to-treat analyses, i.e. with all participants initially assigned to an intervention or control included in their original groups. We also decided that we would exclude from the denominators any deaths or losses unlikely to be associated with trial outcomes. We would treat any other participants lost to follow-up as continuing smokers. We also planned to note any adverse events or side effects and deaths in the Results section. Where data were available, we planned to conduct a meta-analysis of the incidence of serious adverse events, taking those randomised as the denominator and including events up to thirty days after the end of treatment.

We planned a sensitivity analysis restricting the denominator to those known to have taken at least one dose of treatment/intervention. For meta-analysis, we planned to use the random-effects model for the calculation of pooled estimates, and random-effect hazard ratios for mortality/survival rates. For events indicating benefit, i.e. cure, sputum smear conversion, smoking cessation, a RR greater than one indicates a benefit of the intervention. For events that are undesirable, i.e. failure, loss to follow-up and death, a RR less than one indicates a benefit of intervention. For cluster-RCTs, we planned to combine adjusted estimates with individual trial estimates for meta-analysis, using the inverse variance method.

### Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analyses where appropriate, to explore the impact of different variables on the findings of the review. This helps to identify and investigate unexplained sources of heterogeneity. Possible factors for subgroup analysis were:

- Category of TB
- Varying grades and types of smoking (cigarette, bidi, cigar, etc.)
- Types of SCI

### Sensitivity analysis

We planned to perform sensitivity analyses to test the robustness of estimates across different eligibility criteria, such as participants, interventions, comparators, outcome characteristics and methodology in study designs. We also planned to use sensitivity analysis to examine the impact of data characteristics, such as level of

measurement (continuous or ordinal), time to event, correlation coefficients from cluster or cross-over trials, and analysis methods.

# RESULTS

## Description of studies

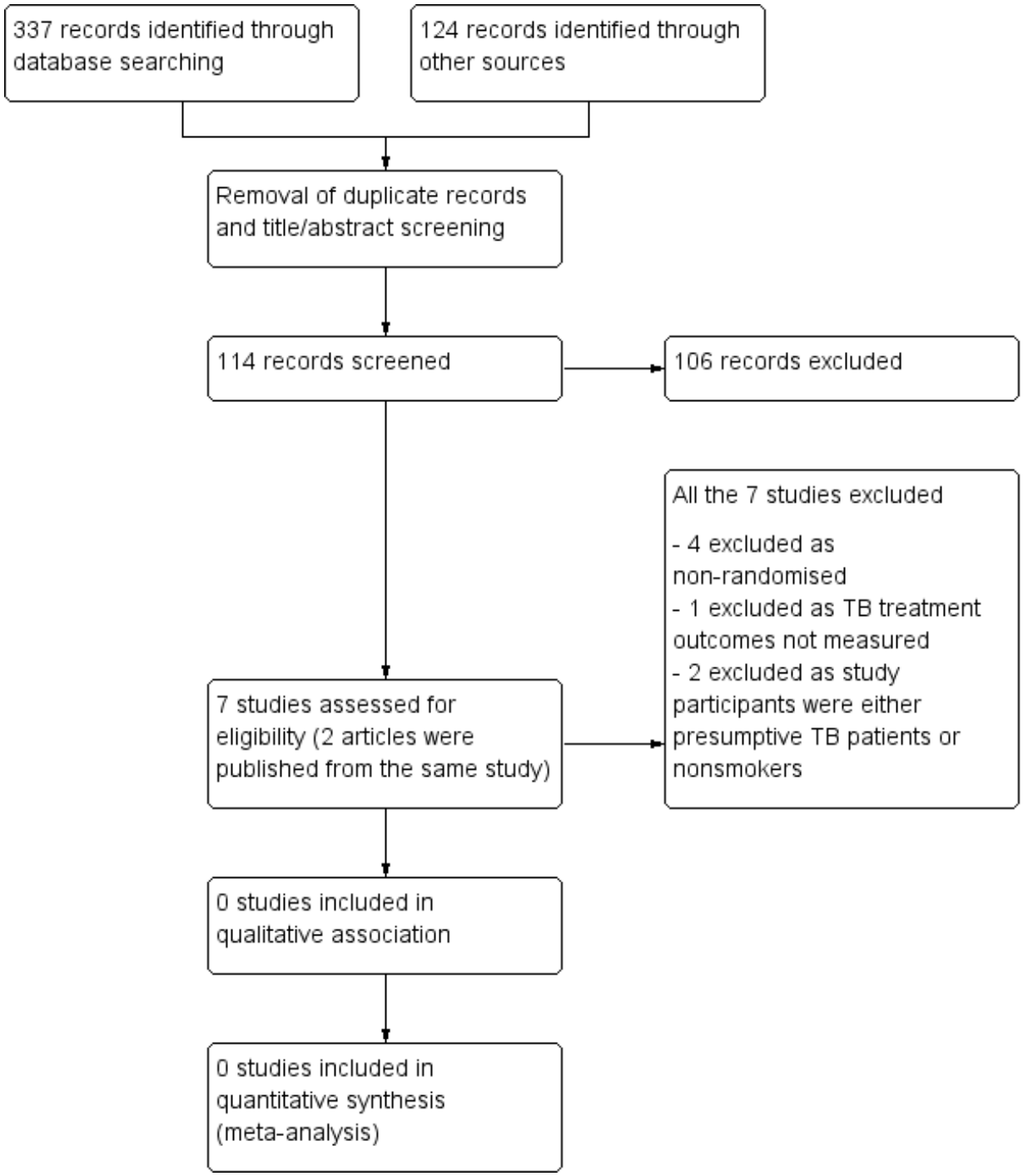
No randomised controlled trials met the inclusion criteria. There are ongoing trials aiming to measure the effectiveness of SCIs on pulmonary TB treatment outcomes. We hope to assess them for inclusion in the next update of this review.

This 'empty' review (i.e. no included studies) discusses findings of the nonrandomised trials and observational studies that were conducted to study the effect of SCIs on TB treatment outcomes.

### Results of the search

Our search of the Cochrane Tobacco Addiction Group Specialised Register, Ovid MEDLINE**,** PubMed MEDLINE and EMBASE yielded 17, 115, 120, and 72 records respectively. The number of additional records identified through searches of conference proceedings, reference lists of the included articles, ICTRP, mRCT, theses and dissertation databases, TRIP, and others was 340. After removal of duplicates, we screened 114 records using the eligibility criteria, and excluded 106 records which did not meet them. We assessed eight full-text articles for eligibility, but found none to be eligible for inclusion into our review (Figure 1). We provide reasons for exclusion below and in the Characteristics of excluded studies table.

**Figure 1. Figure 1. Flow of information through different phases of the systematic review**



### Included studies

No randomised controlled trials met the inclusion criteria

### Excluded studies

After initial screening, we assessed eight articles for eligibility through review of the full-text articles. Of these eight articles, two articles had published different subsets of results from the same study (Awaisu 2011); therefore we considered seven studies for eligibility. From these, we excluded four studies due to the nonrandomised nature of participant allocation (Awaisu 2011; Campbell 2014; El Sony 2007; Kaur 2013). Additionally, the outcome measured in Awaisu 2011 was health-related quality of life. Campbell 2014 and Kaur 2013 measured the tobacco quit rate or abstinence rate. Although Louwagie 2014 was an RCT, we excluded it because TB treatment outcomes were not measured. We excluded the remaining two studies primarily because of the participants in the trial. In Siddiqui 2013, presumptive TB patients were the study participants. In Safdar 2015, nonsmoking TB patients constituted the study group. In this study, the outcome measure was reduction in exposure to secondhand smoking among TB patients after a behavioral intervention.

### Risk of bias in included studies

No randomised controlled trials met the inclusion criteria.

### Effects of interventions

No randomised controlled trials met the inclusion criteria.

## DISCUSSION

No studies met the eligibility criteria for inclusion in this review, and this is therefore an 'empty' review. However, we did identify five ongoing studies that may be eligible for inclusion in the review when it is updated. We are confident that we identified all relevant literature, as we followed the rigorous search guidelines detailed in the *Cochrane Handbook for Systematic Review of Interventions* (Higgins 2011). The search strategies developed by the review authors were verified by our Cochrane Group Trials Search Co-ordinator and we searched a range of sources (standard databases, trial registries and grey literature). These searches were all up to date at the time of submission to the editorial process (July 2015).Three of the review authors have independently checked the search results and scanned them for eligibility.

There are currently no guidelines regarding the reporting of 'empty' reviews (Yaffe 2012). We present our Discussion based on the available evidence from studies that did not meet our eligibility criteria, but nevertheless addressed a similar research question: tobacco cessation interventions and TB. There is evidence that tobacco smoking worsens TB treatment outcomes as suggested by the greater odds of sputum non-conversion at two months (Maciel 2013; Nijenbandring de Boer 2014), higher incidence of treatment delay, loss to follow-up, failure, reinfection and mortality among smokers compared to nonsmokers (Slama 2007a) reported in observational studies. Far less research has been carried out examining the effectiveness of SCIs on TB treatment outcomes; hence the need for high-quality research and this review. However, Wen 2010 concluded, based on a cohort of adults in Taiwan, that not only does smoking cessation reduce the risk of TB but also reduces TB mortality by one third.

We found only two experimental studies (Awaisu 2011; El Sony 2007) that addressed the question our review seeks to investigate, but these studies did not randomly assign their participants, and so did not meet the eligibility criteria agreed for our review. Other studies addressed similar research questions but failed to measure the primary outcome under consideration. They studied the effect of SCIs on intermediate outcomes such as smoking quit rates and the feasibility of the integration of an SCI programme into a TB control programme.

#### Studies reporting TB treatment outcomes

Awaisu 2011 (N = 120) was a quasi-experimental study. The authors developed an integrated package of SCI and directly observed short course treatments (DOTS) (SCIDOTS group) to be delivered to the intervention arm alongside a control arm, which received usual standard care, i.e. DOTS alone (DOTS group). Tobacco cessation among participants was ascertained by measurement of exhaled carbon monoxide, a valid objective method. At the end of the six-month DOTS regimen, the SCIDOTS group had significantly higher sputum smear conversion than the DOTS group (100.0% versus 93.9%; P = 0.043). Radiological resolution of lung lesions was also significantly better among the intervention group compared with the control group (67.5% versus 34.8%, respectively; P = 0.001). The loss to follow-up rate was significantly lower among the SCIDOTS group compared with the DOTS group (2.5% versus 15.2%; P = 0.031), and the cure rate was significantly higher among the intervention group (62.5% versus 34.8%; P = 0.031). We noted similar findings in participants who required treatment beyond six months.

However, the seemingly positive results of the study need to be interpreted in the light of its methodological problems. All the study participants were smokers who were newly diagnosed with

TB (the type of TB was not mentioned), and were recruited voluntarily. The authors allocated participants to trial arms based on the Transtheoretical Model (also known as the Stages of Change model) (DiClemente 1991), i.e. the participants were allowed to choose the arm of the study into which they wanted to enrol themselves. This could have led to selection bias, with the more health-conscious and thus otherwise healthier participants enrolled in the intervention arm, leading to the apparently better treatment outcomes. A randomised allocation would have overcome this bias. The authors did not attempt to compare the characteristics of the dropouts and the participants, and significant differences between these could also have indicated bias in the study results. Also, we cannot rule out the chance of bias due to a difference in the baseline nicotine dependence between groups in this study.

El Sony 2007 (N = 513) mainly assessed the feasibility of integrating an SCI into a TB control programme. This was a quasi-experimental study with intervention at cluster level, i.e. primary and respiratory care centres in Sudan. The study also assessed the effect of the intervention package on TB treatment outcomes. This study did not find any statistically significant difference in the treatment outcomes between the control and intervention centres, but it did find a statistically significant difference in treatment outcomes (cure and loss to follow-up) between enrolled and non-enrolled TB patients. The sample size calculation and randomisation techniques employed in the study are not clear. Convenience sampling was used to select the study areas. As no eligible patients refused to take part in the study (N = 1177), it was not clear how they selected and recruited the 513 participants. In addition, the intervention and control groups had significant baseline differences in terms of both education and current tobacco use.

The SCI by El Sony 2007 was very basic, consisting of brief behavioural counselling based on open-ended questions. Awaisu 2011, however, had designed a comprehensive SCI package that consisted of personalised behavioural counselling, educational materials, and refills of drug prescriptions related to smoking cessation. Smoking cessation was self-reported in El Sony 2007, while it was objectively measured by Awaisu 2011 using exhaled carbon monoxide measurements. Neither study could rule out the Hawthorne effect (Wickstrom 2000), induced by the more frequent interactions of the health workers/study staff with the participants in the intervention arm. Passive smoking and other forms of exposure to environmental smoke such as cooking fuel, air pollution, etc. were not accounted for in either study (Awaisu 2011; El Sony 2007).

**Studies reporting tobacco abstinence rates and/or QOL**

Among studies investigating the effectiveness of SCI on outcomes such as abstinence rates and quality of life (QOL) in people with TB, Awaisu 2011 reports that an integrated TB-tobacco treatment strategy could improve overall QOL outcomes among smokers with TB. Siddiqui 2013 concluded that behavioural support alone or in combination with bupropion is effective in promoting cessation in smokers who were presumptive TB patients. This study included presumptive TB patients rather than participants on TB treatment, thus addressing a more general study population. TB treatment outcomes were therefore not assessed. Other studies that included SCIs in the form of brief advice to stop smoking alongside TB treatment were Campbell 2014 and Kaur 2013. In the former study, they found that in contrast to the control group, in which none had quit smoking, 39% of the intervention group had quit. The latter study was a single-stage quasi-experimental cluster trial where all TB patients belonging to a district were given brief advice during their treatment for TB, regardless of the type of TB and tobacco use (smoke or smokeless). This study found that around 67% of the participants quit tobacco at the end of treatment due to brief advice. The study did not assess any TB treatment outcomes.

**Studies reporting the feasibility of the integration of SCI into TB control programmes**

The overburdened health staff in developing countries, who operate under infrastructure constraints, need to be convinced about the utility of the additional interventions that they are expected to deliver (Slama 2007b). El Sony 2007 stated that before the integration of SCIs into TB programmes it is necessary to ensure that they do not overburden the staff and cripple the otherwise efficiently-functioning TB control programme. They studied the acceptability of the new intervention to staff and patients, in addition to studying the change in staff behaviour over time. They took participant recruitment rates into the trials as an indicator of the acceptability of the intervention to the patients. Both El Sony 2007 and Kaur 2013 reported that the integration of the SCI intervention into an existing TB treatment programme is feasible. They also added that such integration did not lead to deterioration of the existing quality of care offered to TB patients. Kaur 2013 stated that it was indeed cost effective to combine SCIs into TB control programmes, as deduced from their case study. They state that existing infrastructure and manpower could be optimally deployed to deliver SCIs within TB control programmes.

# AUTHORS' CONCLUSIONS

## Implications for practice

There is a high prevalence of tobacco smoking among people with TB, and poor treatment outcomes are more common among smokers. The practice of using pharmacotherapeutic agents alone or in combination with other tobacco cessation interventions among people with TB who are on antitubercular therapy should be based on evidence from RCTs. There is a lack of high-quality evidence that supports the effectiveness of SCIs in improving TB treatment outcomes. There is currently not enough evidence to support the use of SCIs in improving TB treatment outcomes.

However, there appear to be ongoing RCTs that seek to answer this question. We hope to be able to synthesise the evidence from these RCTs in the next update of this review, thus allowing us to create a stronger evidence base for or against the use of SCI in the treatment of TB.

### Implications for research

There are a number of observational studies that have associated smoking with unfavourable short-term TB treatment outcomes. However, there is a need for good-quality randomised controlled trials that assess the effect of SCIs on TB treatment outcomes in both the short and long term. Pharmacological and behavioural SCIs need to be studied for their effectiveness in improving TB treatment outcomes.The SCI package should be designed to be appropriate for the target population. If using existing SCI packages, they should be modified appropriately to suit the target population and healthcare delivery system of the study area. The additional monitoring mechanisms, if any, required for the implementation of the SCI should be clearly documented for feasibility of replication in similar populations. As well as self reporting, smoking cessation should be objectively assessed biochemically.

Gender differences, if any, in the effect of SCIs on TB treatment outcomes may also interest researchers, given the rising numbers of female tobacco smokers worldwide.

Further, the cost effectiveness of different SCIs should be assessed to inform the implementation of cost-effective intervention packages. Establishing such an evidence base would be an essential step towards evaluating the implementation of SCIs into TB control programmes worldwide.

## ACKNOWLEDGEMENTS

Authors acknowledge the assistance provided by Dr. Monaz Mehta, Dr. Nicola Lindson-Hawley and Ms. Lindsay Stead of the Cochrane Tobacco Addiction Group. The authors also acknowledge the comments given by the peer reviewers.

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* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Awaisu 2011 | The SCIDOTS project including TB treatment outcomes. Excluded as it is a non-randomised trial |
| Campbell 2014 | This study was neither an RCT nor did it measure the TB treatment outcome. It measured tobacco quitting among TB patients |
| El Sony 2007 | Not a randomised trial. Investigators used convenience sampling and the intervention was allocated at the primary or respiratory care centre level |
| Kaur 2013 | A single-stage quasi-experimental cluster trial with brief advice as the intervention for tobacco cessation. Tobacco quit rate is the outcome assessed and TB treatment outcomes were not assessed |
| Louwagie 2014 | The study did not measure TB treatment outcomes. It focused only on tobacco abstinence rates |
| Safdar 2015 | Participants were nonsmoking TB patients who were provided with a brief intervention to reduce their exposure to secondhand smoke in their home |
| Siddiqui 2013 | Cluster-randomized controlled trial of presumptive TB patients; however end points were not TB treatment outcomes. The primary end point of the study was continuous abstinence |

### Characteristics of ongoing studies *[ordered by study ID]*

**CTRI/2013/07/003830**

| | |
|---|---|
| Trial name or title | Evaluation of different strategies (pharmacologic intervention versus enhanced motivation vs standard motivation) for smoking cessation in TB patients under treatment in the RNTCP |
| Methods | Study design: cluster-randomised, open-label trial<br>Permuted block randomisation, fixed<br>Country: India<br>Setting: DMCs in 2 districts |
| Participants | Men and women<br>18 - 70 years<br>Current smoker with smear positive TB |
| Interventions | Intervention 1: bupropion SR 150 mg tablet oral twice daily for 7 weeks (pharmaceutical)<br>Intervention 2: enhanced counselling (behavioural)<br>Control intervention 1: standard counselling (behavioural) |

**CTRI/2013/07/003830** (*Continued*)

| | |
|---|---|
| Outcomes | Primary outcomes: smoking cessation at 2nd and 6th month<br>Secondary outcome: TB treatment cure at 6th month |
| Starting date | August 2013 |
| Contact information | Dr. Ramesh Kumar<br>dr.rameshkumar@yahoo.co.in |
| Notes | Trial registration: CTRI/2013/07/003830<br>Estimated study completion date: 2016 |

**Goel S**

| | |
|---|---|
| Trial name or title | Effect of smoking cessation intervention package on treatment outcomes in pulmonary TB patients: a cluster-randomised controlled trial |
| Methods | Study design: Cluster-randomised trial defined at the level of TB-designated microscopy centres (DMC). 16 DMCs were randomised into 2 groups equally as control and intervention<br>Country: India<br>Setting: TB-designated microscopy centres (DMC) |
| Participants | Men and women<br>841 diagnosed TB patients recruited,185 of whom are smokers; 83 were randomised to control arm and 102 to the intervention arm<br>Recruitment method: sequential |
| Interventions | Intervention: The intervention package suggested by the International Union Against Tuberculosis and Lung Disease in 'Smoking Cessation and Smoke-free Environments for TB Patients' consists of brief advice and assistance to quit tobacco in the form of behavioural or pharmaceutical interventions as found appropriate<br>Control: standard care under DOTS |
| Outcomes | Primary outcomes: TB treatment outcomes, namely cure, completion, mortality, loss to follow-up and failure<br>Secondary outcome: smoking quit rate |
| Starting date | January 2013 |
| Contact information | sonugoel007@yahoo.co.in |
| Notes | Trial registration: unknown<br>Estimated study completion date: unknown |

**IRCT2013062613783N1**

| | |
|---|---|
| Trial name or title | Determining efficacy of smoke cessation programme on quit rate, immunological response and treatment outcome in new pulmonary TB patients: a clinical trial |
| Methods | Study design: randomised, controlled, unblinded trial<br>Country: Iran<br>Setting: National Research Institute of Tuberculosis and Lung Disease (NRITLD), Tehran |
| Participants | Men and women<br>18 - 90 years<br>New active pulmonary TB patients (both sputum smear positive and negative)<br>Smokers and nonsmokers |
| Interventions | Intervention 1: cessation consultation and pharmacotherapy: cessation consultation consists of Advice, Assist and Arrange. 4 counselling sessions are held during the first 2 weeks. Patients also receive sustained release Bupropion 150 mg twice daily for 9 weeks<br>Intervention 2: brief advice counselling<br>Control 1: smokers given regular care for TB alone<br>Control 2: nonsmokers given regular care for TB alone |
| Outcomes | Primary outcomes: sputum smear conversion and TB treatment outcome at 2, 4 and 6 months |
| Starting date | August 2013 |
| Contact information | Prof. Mohammad Reza Masjedi<br>mrmasjedi@gmail.com<br>nritld.sbmu.ac.ir |
| Notes | Trial registration: IRCT2013062613783N1<br>Estimated study completion date: unknown |

**NCT01517022**

| | |
|---|---|
| Trial name or title | Intensive Smoking-cessation Versus Basic Smoking-cessation Advice in Smear-positive Patients With Pulmonary Tuberculosis |
| Methods | Study design: described as both an observational prospective case-control study and a randomised controlled trial<br>Country: India |
| Participants | Recruitment method: probability sample<br>Aims to recruit 600 participants<br>Men and women<br>18 to 65 years<br>New smear-positive TB patients who smoke at least 10 cigarettes or bidis per day |
| Interventions | Intervention: nicotine replacement therapy (pharmaceutical)<br>Control: basic smoking advice along with routine DOTS treatment |

**NCT01517022** (*Continued*)

| | |
|---|---|
| Outcomes | Sputum smear conversion (weekly sputum smear and culture testing up to 8 weeks followed by sputum smear and culture testing at 6xth month) |
| Starting date | November 2010 |
| Contact information | Prof. SK Sharma, AIIMS, New Delhi, India<br>sksharma.aiims@gmail.com |
| Notes | Trial registration: NCT01517022<br>Estimated study completion date: March, 2016 |

**NCT02238405**

| | |
|---|---|
| Trial name or title | A Controlled Smoking Cessation Trial and Prospective Cohort Study of Tuberculosis (TB) Treatment Outcomes |
| Methods | Study design: randomised, controlled, open-label trial with observational analysis comparing quitters and nonquitters<br>Country: Pakistan<br>Setting: TB treatment clinic |
| Participants | Men<br>18 years and above<br>Pulmonary TB patients<br>Current smoker or smoker within past 6 months |
| Interventions | Intervention: Intensive anti-smoking counselling (behavioural)<br>Control: current standard care |
| Outcomes | Primary outcomes: smoking cessation rate at 1 - 6 months and at post-TB treatment<br>Secondary outcomes: negative TB treatment outcome (death, treatment failure, relapse, required prolongation of TB therapy) |
| Starting date | October 2014 |
| Contact information | Ayesha A Khan, akhan6@jhu.edu |
| Notes | Trial registration: NCT02238405<br>Estimated study completion date: July, 2016 |

## DATA AND ANALYSES

This review has no analyses.

## APPENDICES

### Appendix 1. Database Resources

We searched the following databases.
1. CENTRAL including Cochrane Tobacco Addiction Group Specialized Register **(The Cochrane Library 2015, Issue 7)** .
2. Ovid MEDLINE **(1946-May Week 30, 2015)** .
3. Pubmed MEDLINE **(till Week 30,2015)** .
4. EMBASE **(1974- Week 30, 2015)** .
5. ISI Web of Science with Conference Proceedings.
6. ClinicalTrials.gov (clinicaltrials.gov/) i.e., National and international trials registers.
7. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch/ ).
8. metaRegister of Controlled Trials (mRCT) (controlledtrials.com/mrct/) and Trials results registers.
9. Search Engines like Google Scholar and Turning Research into Practice (TRIP) database.
10. Dissertations and theses databases **(1960 onwards)** .
11. Other reviews, guidelines and reference lists as sources of studies

### Appendix 2. MEDLINE search strategy

Register strategy plus topic terms
1. RANDOMIZED-CONTROLLED-TRIAL.pt.
2. CONTROLLED-CLINICAL-TRIAL.pt.
3. PRAGMATIC-CLINICAL-TRIAL.pt.
4. CLINICAL-TRIAL.pt.
5. Meta analysis.pt.
6. exp Clinical Trial/
7. Random-Allocation/
8. randomized-controlled trials/
9. double-blind-method/
10. single-blind-method/
11. placebos/
12. Research-Design/
13. ((clin$ adj5 trial$) or placebo$ or random$).ti,ab.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).ti,ab.
15. (volunteer$ or prospectiv$).ti,ab.
16. exp Follow-Up-Studies/
17. exp Retrospective-Studies/
18. exp Prospective-Studies/
19. exp Evaluation-Studies/ or Program-Evaluation.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
20. exp Cross-Sectional-Studies/
21. exp Behavior-therapy/
22. exp Health-Promotion/
23. exp Community-Health-Services/

24. exp Health-Education/ 25. exp Health-Behavior/
26. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. smoking cessation.mp. or exp Smoking Cessation/
28. "Tobacco-Use-Cessation"/
29. "Tobacco-Use-Disorder"/
30. Tobacco-Smokeless/
31. exp Tobacco-Smoke-Pollution/
32. exp Tobacco-/
33. exp Nicotine-/
34. ((quit$ or stop$ or ceas$ or giv$) adj5 smoking).ti,ab.
35. exp Smoking/pc, th [Prevention & Control, Therapy]
36. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 [A category smoking terms]
37. exp Smoking/ not 36 [B category smoking terms]
38. 1 or 2 or 3 [Likely CT design terms; RCTs, CCTs, Pragmatic trials]
39. 36 and 26 [A category smoking+all design terms]
40. 36 and 38 [A category smoking terms+likely CT design terms]
41. (animals not humans).sh. [used with 'not' to exclude animal studies for each subset]
42. 37 and 26 [B category smoking+all design terms]
43. (42 and 38) not 41 [Set 3: B smoking terms, likely CT design terms, human only]
44. 39 not 40 not 41 [Set 2: A smoking terms, not core CT terms, human only]
45. (36 and 38) not 41 [Set 1: A smoking terms, likely CT design terms, human only]
46. exp Tuberculosis/ or tuberculosis.mp or exp Antitubercular drugs/
47. 45 and 46 [Set 1 and topic]
48. 44 and 46 [Set 2 and topic]
49. 43 and 46 [Set 3 and topic]
50. 47 or 48 or 49 [All smoking and topic]

## Appendix 3. EMBASE search strategy

Register strategy plus topic terms
1. random$.ti,ab. Insert Search Statement
2. factorial$.ti,ab.
3. (cross over$ or crossover$ or cross-over$).ti,ab.
4. placebo$.ti,ab.
5. (double$ adj blind$).ti,ab.
6. (single$ adj blind$).ti,ab.
7. assign$.ti,ab.
8. allocat$.ti,ab.
9. volunteer$.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE-BLIND PROCEDURE.sh.
14. or/1-13
15. smoking cessation.mp.
16. exp smoking cessation/ or smoking cessation program/
17. exp smoking-/
18. 17 and (((quit$ or stop$ or ceas$ or giv$ or prevent$) adj3 smok$) or cigarette$).ti,ab.
19. exp passive smoking/
20. exp smoking habit/
21. smokeless tobacco/

22. 15 or 16 or 18 or 19 or 20 or 21
23. 14 and 22
24. exp Tuberculosis/ or tuberculosis.mp or exp Antitubercular drugs/
25. 23 and 24

## CONTRIBUTIONS OF AUTHORS

Kathiresan Jeyashree (KJ) - Conception of the review, preparation of the first draft of the protocol and review, quality assessment of the included papers, preparation of the first draft of the review and revision of the review draft.

Soundappan Kathirvel (SK) - Revision of the protocol draft, quality assessment of the included papers, revision of the review draft.

Hemant D Shewade (HDS) - Revision of the protocol draft, quality assessment of the included papers, preparation of the first draft of the review and revision of the review draft.

Harpreet Kaur (HK) - Development of search strategy, literature search from various sources and compilation.

Sonu Goel (SG) - Topic expert, revision of the protocol, critical analysis of the results of the review.

## DECLARATIONS OF INTEREST

KJ - None known

SK - None known

HDS - None known

HK - None known

SG - None known

## SOURCES OF SUPPORT


### Internal sources

- None, Other.

### External sources

- None, Other.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Smoking [adverse effects]; Smoking Cessation [methods]; Treatment Outcome; Tuberculosis, Pulmonary [etiology; *therapy]

### MeSH check words

Adult; Humans