**Manuscript title:** Multicentre Randomised Double-Blind Placebo Controlled Trial of Cytisine for Smoking Cessation in Smokers with Tuberculosis

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**ABSTRACT**

**Background**

Smoking cessation in Tuberculosis (TB) patients is important because it can reduce the high treatment failure and death rates. Cytisine is an effective low-cost treatment for smoking cessation that has not been tested in TB patients. This study aims to assess its effectiveness and safety as a smoking cessation aid in TB patients in Bangladesh and Pakistan.

**Methods**

We conducted a two-arm, parallel, individually randomised, double-blind, placebo-controlled, multicentre trial. Adult pulmonary TB patients were randomised 1:1 to a 25-day treatment regimen with cytisine plus brief behavioural support or placebo plus brief behavioural support; both medications were identical 1.5 mg hard capsules for oral administration and behavioural support was a 15 minute face-to-face session delivered by health workers. Pre-generated block randomisation lists, stratified by trial sites, were used for allocation. An intention to treat analysis was conducted on the primary outcome: biochemically-veriﬁed continuous smoking abstinence at six months post-randomisation. The trial registration number is ISRCTN43811467, International Standard Randomised Clinical Trial Number and it is closed to new participants.

**Findings**

Between June 2017 and April 2018, we randomised 2,472 patients (1,527 in Bangladesh and 945 in Pakistan). At six months, 32.4% (n=401/1239) were continuously abstinent in the cytisine arm and 29.7% (n=366/1233) in the placebo arm (relative risk (RR) 1.09, 95% confidence interval (CI) 0.97 to 1.23, p=0.114). Serious Adverse Events included 91 deaths (49 in the cytisine arm and 42 in the placebo arm). None of these events (including deaths) were attributed to the study medication. Cytisine was well tolerated.

**Interpretation**

Our findings do not support adding cytisine to brief behavioural support when treating tobacco dependence in TB patients.

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# INTRODUCTION

Tuberculosis (TB) affected an estimated 10 million and killed 1.45 million people in 2018 making it one of the most common chronic infectious disorders in the world.[1](https://paperpile.com/c/RgKhRu/KYVl6) In 2017, about 85% of TB deaths occurred in the African and the South- East Asian regions where smoking rates are also very high.[1](https://paperpile.com/c/RgKhRu/KYVl6) In the absence of smoking cessation services to treat nicotine dependence, people in general in these regions remain at risk of premature death and disabilities due to smoking. If the current trends for smoking and TB continue, it is predicted that there will be in excess of 40 million—potentially avoidable—TB-related deaths attributable to smoking by 2050.[3](https://paperpile.com/c/RgKhRu/i80EN) Many smokers in these low- and middle-income countries (LMICs) come into contact with health services creating opportunities to help them quit. Integrating smoking cessation within national and regional TB services in LMICs offers a viable solution to reduce the TB and tobacco-related disease burden.[2](https://paperpile.com/c/RgKhRu/nAAYt)

A TB treatment period of six-months or longer offers opportunities for health professionals to treat tobacco dependence alongside TB. Newly diagnosed TB patients might be more motivated to quit than smokers without TB due to their concerns about their illness and its consequences.[4](https://paperpile.com/c/RgKhRu/BwPgE) By reducing the risk of TB relapses and deaths and by preventing other tobacco-related chronic conditions, the potential health benefits of smoking cessation may be even greater among TB patients than in the general population of smokers.[5](https://paperpile.com/c/RgKhRu/bT0yW) Offering smoking cessation interventions to TB patients should be routine and has been found feasible in many contexts, although this opportunity is rarely taken in low- and middle-income countries (LMICs).[6,7](https://paperpile.com/c/RgKhRu/rDzTv+Y6hqo) The lack of availability of low-cost, effective and safe smoking cessation treatment options in TB patients, among several other barriers, is widely acknowledged.[8](https://paperpile.com/c/RgKhRu/gMHxS),[9](https://paperpile.com/c/RgKhRu/2Pw8w)

Individual counselling, alone and in combination with pharmacotherapy, is an extensively researched and scientifically proven effective strategy for supporting smokers to quit.[10](https://paperpile.com/c/RgKhRu/Hx3D) Our previous trial in 1955 patients attending TB clinics in Pakistan, found two-fifths of smokers attained continuous abstinence at six months with behavioural support offered by health professionals.[5](https://paperpile.com/c/RgKhRu/bT0yW) However, the challenges of delivering 30-40 minutes of behavioural support within routine TB care including resource constraints,[9](https://paperpile.com/c/RgKhRu/2Pw8w) led us to the development of a shorter optimised behavioural support intervention. As well as the provision of behavioural support, there is also substantial evidence on the effectiveness of nicotine replacement therapy (NRT) and medications acting as nicotine receptor partial agonists (bupropion, cytisine and varenicline) in helping smokers in general populations to quit.[11](https://paperpile.com/c/RgKhRu/9og0) Among these, cytisine (a plant-based alkaloid) is recommended as an affordable intervention, especially for LMICs.[12](https://paperpile.com/c/RgKhRu/saxZc) It is 5-10 times cheaper than NRT and varenicline and has been found to be effective in moderate-to-heavy smokers.[12](https://paperpile.com/c/RgKhRu/saxZc) Whether it confers benefits in patients with TB in LMICs is unknown. We set out to investigate the effectiveness and safety of cytisine when added to brief behavioural support in TB patients in Bangladesh and Pakistan.

# METHODS

**Study design**

We conducted a two-arm, parallel, double-blind, placebo-controlled, multicentre, individually randomised trial in 32 health centres across Bangladesh and Pakistan. Sites were designated TB treatment centres run by the respective National TB control Programmes (NTP) and were chosen based on having the required resources and their ability to recruit participants and take part in the research. The sites included 17 sub-district hospitals in Bangladesh and 15 secondary care hospitals in Pakistan and were recruited across both urban and rural areas. Ethics approval was obtained from the University of York (reference no. HSRGC/2016/144/B), UK and in Bangladesh and Pakistan, details can be found in the published protocol.[13](https://paperpile.com/c/RgKhRu/ZBjP3) The trial was conducted in accordance with the principles of the Declaration of Helsinki and the national regulatory requirements. The trial was overseen by an Independent Steering Committee and Data Monitoring Committee (detailed in the Supplementary Appendix).

## Participants

Adults (aged > 18 years in Bangladesh and > 15 years in Pakistan, defined per the NTPs of respective countries) with pulmonary TB diagnosed within the last four weeks, who smoked tobacco on a daily basis with or without smokeless tobacco products and were interested in quitting were enrolled. Using cytisine with certain anti-TB medicines: Para Amino Salicylic Acid (PASA) and streptomycin, reduces its mode of action. Therefore, patients with TB complications (retreatment or drug resistance), or those receiving streptomycin or PASA, as well as those on tobacco dependence medication were excluded. Evidence on the association of smoking with pulmonary TB is strong but such evidence is limited for extrapulmonary TB, therefore, the latter was excluded. Conditions where cytisine is contraindicated (pregnancy/lactating; myocardial infarction/stroke/severe angina within the previous two weeks; high blood pressure not controlled with medication; severe renal impairment requiring dialysis; known diagnosis of schizophrenia or epilepsy) were also excluded on self-report.[13](https://paperpile.com/c/RgKhRu/ZBjP3) All participants provided written informed consent.

## Randomisation and blinding

Patients were randomly assigned in a 1:1 ratio to either cytisine plus behavioural support or placebo plus behavioural support based on blocks of eight patients, stratified by trial sites. Randomisation lists were pre-generated at York Trials Unit by the trial statistician and held securely at country offices for sequential allocation by blinded trial coordinating staff. To ensure double blinding, medication packs were identical and only the code-break envelopes prepared separately for each trial number contained the allocation order, for unblinding in an emergency following the protocol.[13](https://paperpile.com/c/RgKhRu/ZBjP3) Blinded site researchers dispensed cytisine and placebo, both identical in appearance, smell and taste.

## Procedures

A brief behavioural support intervention for smoking cessation was offered to all patients (see Supplementary Appendix for a detailed description). It was delivered by TB health workers in two face-to-face sessions at day 0 (enrolment) and at day 5 (quit date), for 10 and 5 minutes, respectively.[14](https://paperpile.com/c/RgKhRu/DkRC) The standard treatment regimen for cytisine (Desmoxan, Aflofarm) and placebo was a 25-day course with 1.5 mg hard capsules for oral administration, gradually reducing from six capsules (9mg) per day to one capsule (1.5mg) on the last day, with a quit date set for day 5 (see Supplementary Appendix for detailed dosing schedule). The trial medication was dispensed for free by site researchers in two batches: supplies for 7 days at enrolment (day 0), followed by supplies for 18 days at day 5 to complete the course. Clearly labelled colour coded boxes were used for each block of varying regimen (Days 1-3, Days 4-7, Days 8-12, Days 13-16, Days 17-20, Days 21- 24, Day 25) and blister packs were cut out to contain the exact daily dosage. To further simplify the dosing regimen, scheduling cards were completed in the patient’s presence to assist them in remembering when to take the trial medication.

Patients were followed up post-randomisation on day 5, and weeks 5, 9 and 12 and months 6 and 12. Time-points corresponded with routine TB clinic visits, except for day 5 to monitor for adverse drug reactions and month 12 to assess secondary outcomes. Participants were not paid any incentives for follow-up visits but they were paid the transport fare for those visits that fell outside the routine TB care.

**Outcomes**

The primary endpoint was biochemically verified continuous abstinence at 6 months post randomisation (day 0).[15](https://paperpile.com/c/RgKhRu/6AnR2) Abstinence was defined as self-report of not having used more than 5 cigarettes, bidis, water pipe sessions or smokeless tobacco products since the quit date, verified biochemically by a breath carbon monoxide (CO) reading of less than 10 ppm at month 6. A negative urine cotinine test (NicAlert/One Step) was also required for participants reporting smokeless tobacco use at baseline.

Secondary outcomes included: continuous abstinence at 12 months, point abstinence, lapses and relapses at multiple time-points, TB outcomes (TB score based on clinical signs and symptoms,[16](https://paperpile.com/c/RgKhRu/hD2B6) chest X-ray grade, sputum smear microscopy, TB treatment adherence and treatment completion/cure rates), and nicotine dependency -Mood and Physical Symptoms Scale(MPSS), Strength for Urges To Smoke (SUTS) scale and Time to first use of tobacco product after waking.[17](https://paperpile.com/c/RgKhRu/d5AXV) Medication adherence was measured using a pill count and a 7-day recall approach.[18](https://paperpile.com/c/RgKhRu/hMGw0)

Adverse events (AEs) were collected up to week 9 and self-reports recorded on the ‘AEs review’ checklist, compiled from the summary of product characteristics for Desmoxan and previous relevant studies. For definitions and symptoms checklist refer to the trial protocol.[13](https://paperpile.com/c/RgKhRu/ZBjP3) A review was required for patients reporting any moderate to severe symptoms by the site designated independent clinicians, trained in study related AEs, to determine the severity, expectedness and relationship of each event to study treatment. The site researchers notified all serious adverse events to the country coordinating office within 24 hours of becoming aware of an event, who in turn notified the York trial team within (a further) 24 hours. Medically qualified staff at the country coordinating centres confirmed the ‘causality’ and ‘expectedness’ and classified these events using the Medical Dictionary for Regulatory Activities (MedDRA).[13](https://paperpile.com/c/RgKhRu/ZBjP3)

Data were initially collected on paper case report forms (CRFs) and then checked and entered at the country level through a web interface into a central trial database with inbuilt validation rules, hosted by York Trials Unit. Data were extracted periodically by the trial statisticians for the purpose of trial coordination and reporting to the independent oversight committees. Queries were resolved with country trial teams on an ongoing basis.

## Statistical analysis

The trial had 80% power to detect a 6% difference in 6-month continuous abstinence rates between cytisine and placebo arms (i.e. 47% vs 41%), based on cessation rates obtained in previous trials.[7,19](https://paperpile.com/c/RgKhRu/Y6hqo+p8hJu) A total of 2,148 patients (1,074 in each arm) were required; assuming an attrition rate of 10%,[7](https://paperpile.com/c/RgKhRu/Y6hqo) which gave a target recruitment of 2,388 patients (1,194 in each arm).

The number and proportion of abstinent participants were reported by trial arm. The group difference was represented by the risk difference (RD) and relative risk (RR) with 95% confidence intervals (CIs). A *p*-value for the effect of allocation was derived using logistic regression, with trial sites included as random-effects using robust standard errors. Missing primary outcome data were treated as a negative outcome, i.e. continuing smoking. Any primary outcome data collected >4 weeks before or after the 6-month follow-up were also treated as a negative outcome. Secondary outcomes were analyzed in the same manner. Sensitivity analyses of the primary outcome included: adjustment for baseline nicotine dependency, age, gender and form of tobacco use. Exploratory subgroup analyses were conducted by age, gender, form of tobacco use, TB severity, country and socioeconomic status. TB outcomes (continuous) and nicotine dependency were analyzed using linear mixed-effect regression models for all available time points. The number of adverse events (serious and non-serious), patients with any adverse event and adverse events per patient were reported by trial arm and compared using a chi-squared test. The study medication adherence was categorized as good (≥80%), moderate (≥50%) and poor (<50%),[13](https://paperpile.com/c/RgKhRu/ZBjP3) based on the number of days participants self-reported to have taken medications as prescribed.

Costs of treatment for behavioural support and trial medications were collected in local currencies and converted using Purchasing Power Parity (PPP) factor to pool the results across countries. Placebo medications were considered at zero cost. Costs were presented in PPP US$ 2017 values.

Analyses were prespecified and followed the intention-to-treat principle. Two-sided *p* values of <0.05 were considered to indicate statistical significance. Analyses were performed using Stata/SE version 16.0.

The trial is registered with International Standard Randomised Clinical Trial Number, ISRCTN43811467.

**Role of the funding source**

The funder of the study and Aflofarm had no influence on the design, data collection, data analysis, data interpretation or writing of the report. The authors assume responsibility for the accuracy and completeness of this report; the corresponding author had final responsibility for the decision to submit for publication. Access to partial anonymised datasets from the study can be provided upon request to the Chief Investigator.

# RESULTS

## Patient population

Between June 2017 and April 2018, 2,472 patients (1,527 from 17 sites in Bangladesh; 945 from 15 sites in Pakistan) were enrolled and randomly assigned to receive cytisine (1239) or placebo (1233) (Figure 1; Figure S1). Of these, 2272 (92%) patients, 1142 (92%) in cytisine and 1130 (92%) in placebo groups, completed the 6-month follow-up (Figure 1). Baseline characteristics were balanced between the two arms (Table 1). The participants were predominantly male (99%), smoked on average 11 cigarettes per day for the last 23years, with only one-quarter reporting any past quit attempts.

## Primary endpoint

In the cytisine and placebo arms, 675 (54.5%) and 644 (52.2%) participants reported continuous abstinence, which was biochemically-verified in 401 (32.4%) and 366 (29.7%) participants, respectively. A risk difference of 2.7% in favour of cytisine (95%CI -0.96 to 6.33) and a risk ratio of 1.09 (95%CI 0.97 to 1.23) were observed; however, this did not achieve statistical significance, see Table 2. Overall, in patients self-reporting continuous abstinence at 6 months, only 58% (767/1322) were biochemically verified. As a CO cut-off of less than 10 ppm was used for biochemical verification of self-reports of abstinence, participants reporting continuous abstinence at 6 months post-randomisation with a CO reading of 10ppm or more, could not be verified. We regarded these participants as not abstinent; their high CO reading indicated that they were most likely still smoking despite reporting abstinence.

The analysis remained robust to additional adjustments for: (i) baseline level of nicotine dependence; (ii) age, gender and form of tobacco use, with similar treatment effect coefficients and 95% CIs; (iii) excluding the 70 patients who died before 6 months follow-up and for whom a trial outcome of continued smoking status was imputed; and (iv) a complete case analysis further excluding 170 patients with missing data (Table S1). Reasons for missing data primarily related to loss to follow-up or missing biochemical verification data.

## Secondary outcomes

Treatment group differences for self-reported point abstinence favoured cytisine over placebo; 5 weeks: RD 4.40, 95%CI 0.54 to 8.27; 12 weeks: RD 3.14, 95%CI -0.79 to 7.07; 6 months: RD 4.42, 95%CI 0.58 to 8.26; 12 months: RD 3.32, 95%CI -0.38 to 7.02 (Table 2). A smaller benefit (RD 2.64, 95%CI -0.71 to 5.52) was seen for cytisine for biochemically verified continuous abstinence at 12 months, which was not statistically significant. Of those participants who were abstinent at 5 weeks, similar proportions (RD 0.80, 95%CI -1.2 to 2.7) lapsed early in the two arms (Table S2). Rates of late lapse between 5 and 12 weeks were also similar (RD 0.05, 95%CI -1.6 to 1.7) between arms.

Treatment success rates (defined as ‘cured’ or ‘completed treatment’) were high, with 89.5% and 81.4% success in the cytisine arm and 91.2% and 83% in the placebo arm, at 6 and 12 months, respectively (Table 3). TB scores, based on clinical signs and symptoms, dropped from 3.4 at baseline to 1.0 at 12 months in both treatment arms (Figure S2, Tables S3 and S4). Similar non-differential trends were observed in the outcomes of sputum smear microscopy, TB treatment adherence and chest X-ray reports (Tables S5, S6 and S7). We observed similar trends in both arms for MPSS (Figure S3, Table S8) and SUTS scale (Figure S4, Table S9). Self-reported medication compliance was high (>90%) and balanced across both arms (Table S10). Reasons for withdrawals from treatment and non-compliance are listed in Tables S11 & S12.

## Subgroup analyses

Results of the subgroup analyses are presented in Figure S5. There were insufficient numbers of females (n=24) to undertake meaningful gender subgroup analysis. The absolute difference in quit rates among those who smoked only (excluding smokers who also used smokeless tobacco) was small but not statistically significant (34% cytisine v 31% placebo, RR 1.11: 95% CI 0.99 to 1.25). Quit rates among dual users (smoked and smokeless tobacco at baseline) were found to be higher in the placebo arm than for those who only smoked tobacco (*p*=0.024 for the interaction with allocated treatment). Both smoked and smokeless self-reported tobacco use rates were higher in the cytisine arm among smokers only (at baseline) while biochemical verification rates were similar. The difference between groups was not reflected consistently at earlier time points, and the number of participants was small (12 quitters among 170 dual users). The quit response to cytisine was slightly higher in Pakistan than Bangladesh, but this was not statistically significant (risk difference 6% vs 1%, *p*=0.118 for the interaction term).

## Cost of cytisine

The mean costs of training health workers and delivering behavioural support were similar between trial arms. The cost of cytisine was PPP US$48.27 (SE 0.36) per participant in the cytisine arm. Overall, the mean costs of intervention were PPP US$60.65 (SE PPP US$0.41) in the cytisine arm and PPP US$12.37 (SE PPP US$0.08) in the placebo arm. The difference between arms was PPP US$48.28 (95% CI PPP US$47.71 to PPP US$48.80), mostly contributed by cost of cytisine.

## Adverse events

The analysis of adverse events was conducted using all patients in the groups to which they had been randomised. Ninety-nine participants: 53 cytisine (4.3%), 46 placebo (3.7%) experienced a total of 184 SAEs (94 cytisine, 90 placebo). This difference was not statistically significant (RR 1.07, 95% CI 0.89 to 1.29; X2(df=1)=0.48, *p*=0.488). SAEs included 91 deaths (49 in the cytisine arm and 42 in the placebo arm). Other SAEs reported more than twice were ‘Difficulty breathing’ (cytisine: 4, placebo: 6), ‘Fever’ (cytisine: 1, placebo: 3), ‘Lung Cancer’ (cytisine: 9, placebo: 6), ‘Myocardial Infarction’ (cytisine: 8, placebo: 5) and ‘Stroke’ (cytisine: 3, placebo: 2). None of these SAEs (including deaths) were attributed to the study medication. Expected and other reported non-SAEs are summarized in Tables S13 & S14. In total, there were 98 (7.9%) cytisine and 86 (7.0%) placebo patients with one or more non-SAEs (RR 1.13, 95% CI 0.86 to 1.50). A full list of serious and non-SAEs is presented in Tables S15 & 16.

**Supplemental smoking cessation activities**

594/2472 (24%) of patients enrolled in the trial sought supplemental smoking cessation advice in one form or another (Table S17), the majority of which was advice on smoking from public hospitals of on average 2.5 instances. The supplemental smoking cessation advice was balanced across the cytisine and placebo arms of the trial.

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| **Panel: Research in context**  **Evidence before this study**  Before planning this trial, we reviewed relevant literature using four key databases i.e., CINAHL, Embase, MEDLINE, the Cochrane Controlled Register of Trials. We searched for publications in English language from the inception of the datasets till June 2020 for randomised controlled trials of smoking cessation interventions conducted in any healthcare setting in low- and middle-income countries (LMIC) in adult smokers with TB. We found two quasi-experimental studies indicating that offering behavioural support to TB patients may result in high quit rates and improve their clinical outcomes. Among these, was our previous smoking cessation trial of behavioural support with and without bupropion conducted in a large sample of patients with suspected and confirmed TB in Pakistan. The study found that behavioural support was seven to eight times more likely to be successful than usual care in achieving smoking abstinence at six months. A higher cessation rate was observed in those with confirmed TB than those with suspected TB. However, no significant advantage of adding bupropion to the behavioural support was observed. We did not find any other smoking cessation trials in TB patients testing pharmacological agents including nicotine replacement therapy, varenicline or cytisine. Our review concluded that while there is good evidence of the effectiveness of behavioural support in helping TB patients quit smoking, to the best of our knowledge, there is no randomised evidence investigating the effects of cytisine for smoking cessation within a TB setting.  **Added value of this study**  We recruited a large sample of TB patients in a two-country multicentre randomised controlled trial to assess the effectiveness of cytisine with behavioural support for smoking cessation compared to behavioural support alone. While we observed high quit rates in both trial arms, cytisine did not offer a clinically or statistically significant advantage for smoking cessation over-and-above behavioural support in the TB population.  **Implications of all the available evidence**  When offered behavioural support, a significant proportion of TB patients quit smoking often more readily than general smokers. Patients who quit are also more likely to recover from TB than those who do not. There is compelling evidence in support of advising and counselling TB patients to quit smoking. However, current evidence does not support adding pharmacological agents to behavioural support in TB patients. More implementation science research is needed to learn how to integrate behavioural support in routine TB care in LMICs. |

# DISCUSSION

Cytisine did not provide a benefit for smoking cessation over-and-above brief behavioural support in patients with TB. The observed difference of 2.7% in 6-month continuous abstinence rates between the two trial arms was less than the expected clinically significant difference of 6%. Moreover, the observed difference was not statistically significant despite an upper limit of 95%CI above 6%. This finding was consistent across cessation outcomes. The adverse events were balanced between the two trial arms. There were no SAEs attributed to study medication and cytisine appeared to be well-tolerated. Follow-up at the primary endpoint (92%) and medication adherence (81%) rates were high and similar in both arms.

A meta-analysis of all cytisine trials (N = 4,216; sample size range: 150 to 1,214 and search year: 2018) showed that smoking cessation rates improved by 75% compared to placebo.[12](https://paperpile.com/c/RgKhRu/saxZc) In addition, a non-inferiority trial found cytisine more effective than NRT.[20](https://paperpile.com/c/RgKhRu/SGTZi) However, the absolute difference in quit rates between cytisine and placebo in our trial was lower than that reported in previous trials, possibly due to certain contextual and population differences. In subgroup analyses, a small, absolute difference in quit rates in favour of cytisine was noted in those who smoked exclusively (34% vs 31% placebo); this was not statistically significant. Contrary to our trial, previous trials were conducted in healthy participants. Our participants were recently diagnosed with pulmonary TB and as part of behavioural support, learned about the association between smoking and their condition. A clinically significant quit rate (29.7%) achieved in our placebo arm indicates our participants' strong motivation to quit. In our previous trial in patients presenting with TB symptoms, 41% quit rates were achieved with behavioural support, the sessions being longer in duration (30-45 minutes) than the current study.7 This difference in intrinsic motivation between specific groups and the general population is also exemplified during pregnancy when high quit rates are achieved with behavioural support alone.[2](https://paperpile.com/c/RgKhRu/EfL1A)1 Another key difference between our participants and those in the previous cytisine trials is the level of nicotine addiction. The means for the number of cigarettes smoked per day in previous cytisine trials were higher (19.3 + 11.9 in Walker et al.[20](https://paperpile.com/c/RgKhRu/ygI3L) and 23.0 + 8.7 in West et al.[2](https://paperpile.com/c/RgKhRu/rXobj)2) than in our trial (11.1 + 8.10). In general, heavy smokers with high nicotine dependence are more likely to benefit from medications[2](https://paperpile.com/c/RgKhRu/krdHF)3 by attenuating their withdrawal symptoms than light smokers.[12](https://paperpile.com/c/RgKhRu/saxZc) Although this was not statistically significant, participants in Pakistan with an average of 12.9 cigarettes per day showed better quit rates for cytisine vs placebo (33% vs 27%) than those in Bangladesh (32% vs 31%) with an average of 9.8 cigarettes per day (Figure 2). Moreover, ours was a pragmatic trial conducted in clinical settings where some loss of efficacy is expected as compared to explanatory trials.

Ours is by far the largest cytisine trial undertaken so far. It is also the first such trial conducted across two countries. Bangladesh and Pakistan were chosen due to existing partnerships with academics and TB programmes, local knowledge and previous experience of conducting trials in these countries. Apart from an earlier small trial (n=171) in Kyrgyzstan,[2](https://paperpile.com/c/RgKhRu/4OwSC)4 this was the only cytisine trial and one of the very few smoking cessation trials ever conducted in LMIC settings. Other strengths were the rigor and quality with which the trial was conducted and the assessments of 12-months quit rates and TB outcomes. Approximately, 42% participants self-reporting continuous abstinence at six months could not be verified biochemically. This is consistent with the accuracy of self-report from other smoking cessation clinical trials[2](https://paperpile.com/c/RgKhRu/cRTr)5 and our previous trial[7](https://paperpile.com/c/RgKhRu/Y6hqo) in presumptive TB patients in Pakistan, where about half (49%) of the self-reports could be biochemically validated. This difference could be explained by multiple mechanisms including social desirability in response to the demand characteristics of being in a smoking cessation trial or simply wanting to avoid stigma that may be associated with continued smoking knowing that it will worsen their TB outcomes,[2](https://paperpile.com/c/RgKhRu/cRTr)5 and poor air quality that is a likely contributor to higher CO levels than the cut-off used.[26](https://paperpile.com/c/RgKhRu/qYaz)

Our trial had some limitations that need to be acknowledged for drawing conclusions. First, our assessment of the trial medication adherence, although using a valid 7-day recall approach, was self-reported.[27](https://paperpile.com/c/RgKhRu/aMHuO) Given the complexity of cytisine’s dosing schedule and anti-TB co-medication, adherence to study medication might have been lower than reported. Although this would not influence the difference between the cytisine and placebo groups, it might still have lowered the overall quit rates across the two groups. Secondly, cytisine’s stability and pharmacovigilance have not been assessed in the temperatures and humidity encountered in South Asia. While we ensured medication storage conditions were within the manufacturer's recommendations, exposures to high temperatures and/or humidity might have occurred leading to instability and loss of efficacy. Thirdly, our trial was not powered to detect differences in secondary TB outcomes, nor subgroup analysis. Finally, we failed to recruit many women, which may limit the generalisability of our findings. This is however likely to be due to very low smoking prevalence among women in South Asia and may also be due to gender specific barriers in seeking cessation support (e.g. stigma), which need further exploration.[28](https://paperpile.com/c/RgKhRu/FU7zR) Other future research avenues include cytisine’s effectiveness using simplified dosing schedules, in combination with other medications, with intensive behavioural support or without behavioural support. Pharmacovigilance studies are also needed to study cytisine’s stability in a variety of geographical regions. With affordable smoking cessation aids like cytisine under consideration for licensing in western countries, there is a bigger need to evaluate these options for smoking cessation in LMICs and in smoking-attributable disease groups.

In summary, our trial found that adding cytisine to brief behavioural support was not effective for smoking cessation in routine TB care. Health professionals should continue to ask TB patients about their smoking status and offer quitting support in line with current national or international guidance.

# CONTRIBUTORS

OD drafted the manuscript, contributed to study design, conduct and interpretation of findings. AKe contributed to methods and results sections of the manuscript, data management and statistical analysis. AR and AMM managed the study and contributed to interpretation of findings. DK, EK, MB and HE provided insights to study design on aspects of behavioural support implementation, evaluation of its delivery and interpretation of findings. RH, DB, RF, AK, RZ and SM conducted the study in Bangladesh/Pakistan, collected and managed the data in countries and provided critical inputs to data analysis and interpretation. RG contributed to study design, conduct and interpretation of results, and provided supervision and critical input into the analysis. SP and JL designed and conducted the cost analysis. AS provided critical oversight to study design, trial conduct, interpretation of findings and discussion. KS conceptualised the study, contributed to the study design, conduct, interpretation of findings and writing of the manuscript.

All authors provided critical revisions and approved the final manuscript.

# DECLARATION OF INTERESTS

Kamran Siddiqi received a research grant from Pfizer (2015-2017) to study the effects of varenicline (a smoking cessation medicine) on waterpipe smoking cessation. Eva Kralikova reports participation in clinical studies from Pfizer, conference attendance from Pfizer and grants from Pfizer, before and during the conduct of the study. Daniel Kotz received an unrestricted grant from Pfizer in 2009 for an investigator-initiated trial on the effectiveness of practice nurse counselling and varenicline for smoking cessation in primary care (Dutch Trial Register NTR3067; DOI: 10.1111/add.13927).

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# References

1. [WHO. **Global tuberculosis report 2019**.](http://paperpile.com/b/RgKhRu/KYVl6) <https://www.who.int/tb/publications/global_report/en/.> Date accessed: November 14, 2019

2. Slama K, Chiang CY, Enarson DA, et al. **Tobacco and tuberculosis: a qualitative systematic review and meta-analysis**. *Int J Tuberc Lung Dis.* 2007; **11**(10):1049–61.

3. Basu S, Stuckler D, Bitton A, Glantz SA. **Projected effects of tobacco smoking on worldwide tuberculosis control: mathematical modelling analysis**. *British Medical Journal.* 2011; 343.

4. Lawson PJ, Flocke SA. **Teachable moments for health behavior change: a concept analysis**. *Patient Educ Couns*. 2009; **76**(1):25–30.

5. Arcavi L, Benowitz NL. **Cigarette smoking and infection.** *Arch Intern Med.* 2004; **164**(20):2206.

6. Elsey H, Khanal S, Manandhar S, et al. **Understanding implementation and feasibility of tobacco cessation in routine primary care in Nepal: a mixed methods study.** *Implement Sci.* 2016; **11**(1):104.

7. Siddiqi K, Khan A, Ahmad M, et al. **Action to stop smoking in suspected tuberculosis (ASSIST) in Pakistan: a cluster randomized, controlled trial.** *Ann Intern Med.* 2013; **158**(9):667–75.

8. Dogar O, Bullen C, Novotny TE, Siddiqi K. **Smoking cessation and respiratory disease in low-income and middle-income countries.** *Lancet Respir Med.* 2013 Jul; **1**(5):e23–4.

9. Dogar O, Elsey H, Khanal S, Siddiqi K. **Challenges of Integrating Tobacco Cessation Interventions in TB Programmes: Case Studies from Nepal and Pakistan**. *Journal of Smoking Cessation.* 2016; **11** (2):108–15.

10. [Lancaster T, Stead LF. **Individual behavioural counselling for smoking cessation.** *Cochrane Database Syst Rev.* 2017; 3.](http://paperpile.com/b/RgKhRu/Hx3D)

11. Cahill K, Lindson‐Hawley N, Thomas KH, Fanshawe TR, Lancaster T. **Nicotine receptor partial agonists for smoking cessation.** *Cochrane Database Syst Rev.* 2016; 5.

12. Tutka P, Vinnikov D, Courtney RJ, Benowitz NL. **Cytisine for nicotine addiction treatment: a review of pharmacology, therapeutics and an update of clinical trial evidence for smoking cessation.** *Addiction*. 2019; **114**(11):1951-69.

13. Dogar O, Barua D, Boeckmann M, et al. **The safety, effectiveness and cost-effectiveness of cytisine in achieving six-month continuous smoking abstinence in tuberculosis patients-protocol for a double-blind, placebo-controlled randomized trial.** *Addiction*. 2018; **113**(9):1716-26.

14. University of York. **Are you a health professional or manager working with people with TB? If so, this website has a set of materials and resources that will help you to support your patients to quit**. <https://tbandtobacco.org/> Date accessed: June 7, 2020

15. West R, Hajek P, Stead L, Stapleton J. **Outcome criteria in smoking cessation trials: proposal for a common standard**. *Addiction*. 2005; **100**(3):299-303.

16. Rudolf F, Lemvik G, Abate E, et al. **TBscore II: refining and validating a simple clinical score for treatment monitoring of patients with pulmonary tuberculosis.** *Scand J Infect Dis.* 2013; **45**(11):825–36.

17. Baker TB, Piper ME, McCarthy DE, et al. **Time to first cigarette in the morning as an index of ability to quit smoking: implications for nicotine dependence.** *Nicotine Tob Res.* 2007; **9**(Suppl\_4):S555–70.

18. Giordano TP, Guzman D, Clark R, Charlebois ED, Bangsberg DR. **Measuring adherence to antiretroviral therapy in a diverse population using a visual analogue scale.** *HIV Clin Trials.* 2004; **5**(2):74–9.

19. Hajek P, McRobbie H, Myers K. **Efficacy of cytisine in helping smokers quit: systematic review and meta-analysis**. *Thorax.* 2013; **68**(11):1037–42.

20. Walker N, Howe C, Glover M, et al. **Cytisine versus Nicotine for Smoking Cessation.** *N Engl J Med.* 2014; **371**:2353–62.

21. Curry SJ, McBride C, Grothaus L, Lando H, Pirie P. **Motivation for smoking cessation among pregnant women**. *Psychology of Addictive Behaviors*. 2001; **15**(2):126

22. [West R, Zatonski W, Cedzynska M, et al. **Placebo-controlled trial of cytisine for smoking cessation.** *N Engl J Med*. 2011; **365**(13):1193–200.](http://paperpile.com/b/RgKhRu/rXobj)

23. Bader P, McDonald P, Selby P. **An algorithm for tailoring pharmacotherapy for smoking cessation: results from a Delphi panel of international experts.** *Tob Control.* 2009 Feb;**18**(1):34–42.

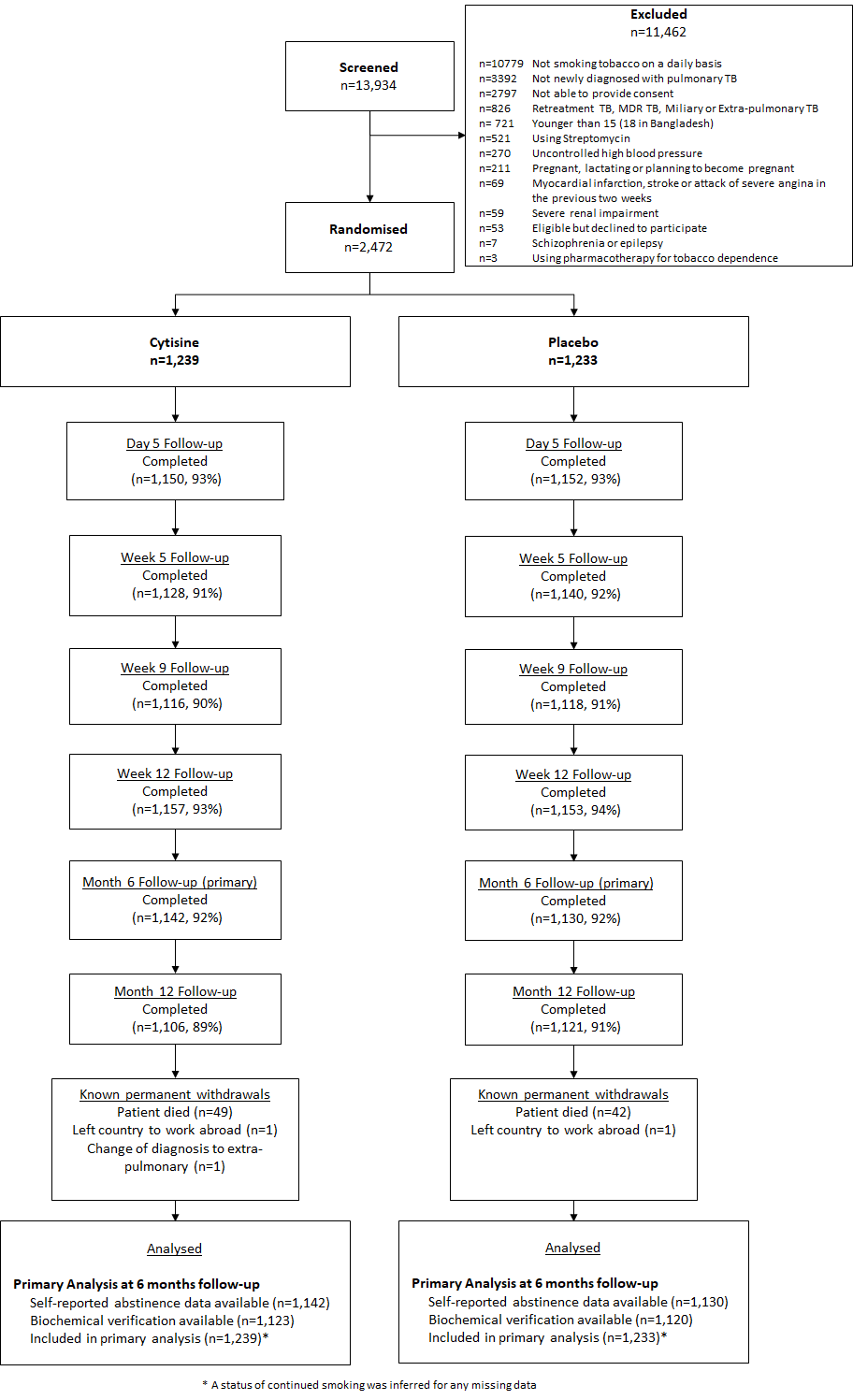
24. Vinnikov D, Brimkulov N, Burjubaeva A. **A double-blind, randomised, placebo-controlled trial of cytisine for smoking cessation in medium-dependent workers.** *J Smok Cessat*. 2008;**3**(1):57–62.

25. Scheuermann TS, Richter KP, Rigotti NA, et al. **Accuracy of self-reported smoking abstinence in clinical trials of hospital-initiated smoking interventions.** *Addiction*. 2017 Dec;**112**(12):2227–36.

26. Kotz D. **Possible reasons for elevated carbon monoxide levels in self-reported ex-smokers**. *Nicotine Tob Res.* 2012 Aug;**14**(8):900–1.

27. [Buchanan TS, Berg CJ, Cox LS, et al. **Adherence to varenicline among African American smokers: an exploratory analysis comparing plasma concentration, pill count, and self-report.** *Nicotine Tob Res.* 2012; **14**(9):1083–91.](http://paperpile.com/b/RgKhRu/aMHuO)

28. Triandafilidis Z, Ussher JM, Perz J, Huppatz K. **An Intersectional Analysis of Women’s Experiences of Smoking-Related Stigma.** *Qualitative Health Research*. 2017; **27**(10):1445-60.



**Figure 1. Recruitment and retention of patients throughout the trial**