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RESEARCH REPORT

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Behavioural support and nicotine replacement therapy for smokeless tobacco cessation in Bangladesh, India and Pakistan: A pilot randomized controlled trial

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Abstract

Background and aims: Smokeless tobacco (ST) use in South Asia is high, yet interventions to support its cessation are lacking. We tested the feasibility of delivering interventions for ST cessation in South Asia.

Design: We used a 2 × 2 factorial design, pilot randomized controlled trial with a duration of 26 weeks, including baseline and follow-up (6, 12 and 26 weeks) assessments.

Setting: Two primary health-care facilities each in Dhaka (Bangladesh) and Karachi (Pakistan) and a walk-in cancer screening clinic in Noida (India) took part.

Participants: Adult daily ST users willing to make a quit attempt within 30 days. Of 392 screened, 264 participants [mean age: 35 years, standard deviation = 12.5, 140 (53%) male] were recruited between December 2020 and December 2021; 132 from Bangladesh, 44 from India and 88 from Pakistan.

Interventions: Participants were randomized to one of three treatment options [8-week support through nicotine replacement therapy (NRT, *n* = 66), a behavioural intervention for smokeless tobacco cessation in adults (BISCA, *n* = 66) or their combination (*n* = 66)] or the control condition of very brief advice (VBA) to quit (*n* = 66).

Measurements: Recruitment and retention, data completeness and feasibility of intervention delivery were evaluated. Biochemically verified abstinence from tobacco, using salivary cotinine, was measured at 26 weeks.

Findings: Retention rates were 94.7% at 6 weeks, dropping to 89.4% at 26 weeks. Attendance in BISCA pre-quit (100%) and quit sessions (86.3%) was high, but lower in post-quit sessions (65.9%), with variability among countries. Adherence to NRT also varied (45.5% Bangladesh, 90% India). Data completion for key variables exceeded 93% among time-points, except at 26 weeks for questions on nicotine dependence (90%), urges (89%) and saliva samples (62.7%). Among follow-up time-points, self-reported abstinence was generally higher among participants receiving BISCA and/or NRT. At

26 weeks, biochemically verified abstinence was observed among 16 (12.1%) participants receiving BISCA and 13 (9.8%) participants receiving NRT.

Conclusions: This multi-country pilot randomized controlled trial of tobacco cessation among adult smokeless tobacco users in South Asia demonstrated the ability to recruit and retain participants and report abstinence, suggesting that a future definitive smokeless tobacco cessation trial is viable.

KEYWORDS
Behavioural support, nicotine replacement, pilot trial, smokeless tobacco, South Asia, tobacco cessation

INTRODUCTION

Smokeless tobacco (ST) refers to a range of tobacco-containing products that are consumed orally or nasally, without burning [1]. ST is consumed by 300 million individuals in 127 countries and contributes to approximately 350 000 deaths annually [2]. Its use is most common in South and Southeast Asia [3], where approximately 85% of global ST-related disease burden is concentrated [2]. In countries such as Bangladesh, India and Pakistan, ST use is considerably higher than in other regions such as North America and Scandinavia [2], and predominantly occurs in people of low socio-economic status [4]. The prevalence of ST use is highest in India (28.6% overall, 29.6% men, 12.8% women), followed by Bangladesh (20.6% overall, 14.3% men and 23% women) and Pakistan (7.7% overall, 11.4 men, 3.7% women) [5]. Throughout the region, ST remains cheap, readily accessible, socially acceptable and poorly regulated [6, 7]. Its initiation and use are heavily influenced by family, friends and socio-cultural norms [8, 9]. Primary health-care is delivered through a mix of public and private health-care providers [10]; however, cessation activity in these settings is low. Only 31–57% of ST users in South Asia receive quit advice from health-care providers [5]. Tobacco cessation services such as national and regional quit-lines, as well as mCessation support, are available in India, although their uptake at population level remains low [11].

South Asian ST products (Data S1) contain high levels of unprotonated nicotine which, combined with additives and flavourings, makes them highly addictive [12]. They also contain elevated levels of tobacco-specific nitrosamines (TSNAs) and heavy metals [12, 13], which are causally linked with oropharyngeal and oesophageal cancers [14, 15], rates of which are the highest in South Asia [16], together with ischaemic heart disease mortality [17], preterm delivery, stillbirths and low birth weight [18]. ST consumption displaces expenditure on basic commodities [19], while ST cessation could improve population-level nutritional status [20].

Article 14 of the World Health Organization Framework Convention on Tobacco Control (WHO-FCTC) [21] underlines the need for evidence-based tobacco cessation [22]. There is currently a lack of standardized cessation methods for ST, a barrier to effective tobacco control [23]. The current evidence, which comprises studies conducted mainly in Europe and North America, suggests that behavioural interventions (counselling from a trained adviser, or 'behavioural support') [24], as well as pharmacotherapy (bupropion, nicotine replacement therapy and varenicline) [25], may be effective in achieving abstinence among ST users. Initial findings from an ongoing review suggest that robust evidence to support ST cessation in South Asian populations is still lacking [26]. Two trials, both in India, have been conducted in the region. A randomized controlled trial (RCT) of varenicline did not demonstrate any difference in biochemically verified abstinence to ST at 12 weeks when compared to a placebo [27], while a cluster RCT of yogic breathing exercises was found to have a small but significant effect on cessation rates at 6 months. The latter trial included smokers and dual users of smoking and ST products [28]. The widespread, culturally ingrained use of a diverse range of highly addictive and toxic ST products and the limited evidence, particularly on interventions that would be contextually appropriate, warrants exploration of ST cessation treatments in the South Asian context.

A theory-based intervention, behavioural intervention for smokeless tobacco cessation in adults (BISCA), has been developed for ST users in the United Kingdom and Pakistan [29], but is yet to be evaluated in an RCT in South Asian settings. Behavioural support's potential may be enhanced with the use of nicotine replacement therapy (NRT), which reduces withdrawal symptoms in individuals trying to quit [30]. In cohort studies of South Asian ST users in England, NRT use was reported as acceptable by ST users, and was associated with higher abstinence at 4 weeks when given alongside behavioural intervention compared to the behavioural intervention alone [31]. Similar uptake and outcomes may be hypothesized for ST users in South Asia. In this paper, we report the findings of a pilot randomized controlled trial of BISCA and NRT (alone and in combination) aimed at testing the feasibility of recruitment and retention, intervention delivery and data collection to inform a future definitive trial for ST cessation in South Asia.

METHODS

Study design

A pilot randomized controlled trial was conducted in Bangladesh, India and Pakistan. We used a 2 × 2 factorial trial design, which offers greater efficiency than parallel arm trials, enabling the simultaneous

	Nicotine Replacement Therapy (NRT)		
Behavioural support intervention (BISCA)		**No**	**Yes**
	No	No treatment (Very Brief Advice-VBA)	NRT only
	Yes	BISCA only	Combined BISCA and NRT

FIGURE 1 A schematic diagram of the 2 × 2 factorial design trial.

investigation of the effects of two or more treatments or their combined effect in the presence of interaction effects [32]. Participants were randomized to receive NRT or BISCA, given alone or in combination. Those who did not receive NRT or BISCA were offered one-off very brief advice (VBA) (Figure 1).

The trial protocol was approved by the Health Sciences Research Governance Committee (HSRGC) at the University of York, Bangladesh Medical and Research Council (ref: BMRC/NREC/2016-2019/961), National Bioethics Committee, Pakistan (ref: 4-87/NBC-355/19/1695), Aga Khan University, Pakistan (ref: 2019-1114-3494), the Health Ministry's Screening Committee, India (ref: 2018-2675) and the Indian Council of Medical Research (ref: NICPR/116/DIR/Ethical/2018-02). Full details of the trial protocol have been published previously [33].

Recruitment, intervention delivery and follow-ups took place in two primary health-care facilities each in Dhaka (Bangladesh) and Karachi (Pakistan) and a cancer screening clinic in Noida (India). All sites were situated in urban areas, meeting the needs of otherwise poorly served communities with a high prevalence of smokeless tobacco use. The chosen facilities were also suitable for trial activities such as recruitment, intervention delivery and follow-up.

Participants and procedures

Eligibility criteria

We included individuals who were:

1. aged > 18 years at the time of screening and recruitment;
2. used ST products daily, i.e. > 25 days per month, during the past 6 months [34];
3. provided written, informed consent (or thumb impressions in the presence of an impartial witness, if unable to write); and
4. expressed motivation to quit ST in the next month.

Dual tobacco users [reporting smoking along with ST use in the past month, or having a carbon monoxide (CO) concentration > 10 parts per million (p.p.m.)] on a breath test (Bedfont piCO smokerlyzer; Maidstone, Kent, UK) [35]), pregnant and/or breastfeeding women, individuals who had suffered from myocardial infarction or stroke in the previous 3 weeks, had unstable angina or were already receiving treatment for tobacco cessation were excluded.

Participant identification and recruitment

Individuals seeking health-care and those attending clinics following community mobilization (public announcements, brochures and leaflets promoting the trial) were screened by a trained researcher using a checklist which elicited information on the eligibility criteria described above and recorded a CO assessment. Eligible individuals received an information sheet and were given sufficient time to ask questions and consult family members before participation. Informed consent was then obtained.

Randomization

Participants were randomized to one of four trial arms in an equal allocation ratio using a country-stratified, permuted block randomization with varying block sizes using R software [36] (additionally stratified by health facilities in Pakistan and Bangladesh). The randomization sequence was generated centrally in York by the trial statistician and shared with the respective trial coordinators, who assigned participants to the interventions. Participants within each country and within each study site were randomized independently into one of the four arms of the study. Opaque, sealed envelopes were used to conceal treatment allocation up to the point of randomization. Blinding of participants and research staff carrying out follow-up assessments was not carried out due to the pilot nature of the study and resource limitations at each site; however, the statistician was blinded until after the main analysis was conducted.

Interventions

Nicotine replacement therapy (NRT)

Participants randomized to receive NRT (with or without BISCA) received an 8-week course of NRT chewing gum from their quit date. The standard dose was 4 mg. Those reporting ST intake within 30 minutes of waking or consuming (ST > 10 times/day) [37] were given a 6-mg dose. An initial 2-week supply, together with instructions, was provided by the cessation adviser [38]; the frequency of consumption was hourly, up to 15 doses a day. Participants received a chart to keep a record of their ST use. Subsequent NRT dispensing was based on consumption for at least 5 days in the previous 7 days. Dosing adjustments were made following participants' experiences in the first week of use. Where available, participants were allowed to choose alternate NRT flavors.

Behavioural intervention for smokeless tobacco cessation in adults (BISCA)

Culturally adapted behavioural support was provided to participants randomized to BISCA (with or without NRT). The BISCA intervention pack comprises an adviser flipbook, a client booklet and a self-help calendar for ST users. It contains 23 activities structured into pre-quit, quit and post-quit sessions. Each activity is informed by evidence-based behaviour change techniques that target ST cessation by modifying the underlying mechanisms of action [29]. Following randomization, participants received at least one pre-quit session(s) focusing upon knowledge of ST ingredients and related harms, self-efficacy and preparing participants for a quit attempt. The quit session, scheduled in the week of the quit date, focused upon strengthening an ex-user identity, identifying triggers and withdrawal symptoms and discussing strategies to manage these. The self-help calendar was provided on this visit. Following the quit session, participants received weekly (up to six) post-quit sessions in which key messages from pre-quit and quit sessions were reinforced, with ongoing support to avoid relapse and minimize withdrawal effects. Participants who reported cessation lapses on 2 consecutive weeks only received VBA through the cessation adviser together with an information leaflet to support their next quit attempt. BISCA was delivered by trained cessation advisers, who were health/allied health professionals and had completed a structured 3-day, five-block training programme focused upon the following topics: ST epidemiology, products and harms, rationales for ST use, benefits of quitting, trial treatment options and their implementation and behaviour change models for planning quit attempts. Intervention delivery was initially face-to-face at the study sites; however, during COVID-19 telephone-based support was provided by the cessation advisers. NRT supplies were dispatched to participants' home addresses. The above modifications were discussed with and approved by the trial monitoring and ethics committees.

Very brief advice

VBA was based on the 3As (Ask, Advise, Act) approach; that is, the adviser asked the participant about ST use, advised them to stop its use and acted by providing a self-help leaflet containing information on quit planning.

Measures

Data collection

A baseline assessment was completed before randomization, and follow-up assessments were carried out at 6, 12 and 26 weeks. A structured questionnaire was used. Participants provided information on socio-demographic variables (age in years), sex (male/female), level of education (no education/primary/middle/secondary/higher secondary/other), tobacco initiation (age in years at first use) [39], current use (type of ST products consumed in past 7 days) [39], ST dependence (using the Fagerström test for nicotine dependence–smokeless tobacco) [mean scores, standard deviation (SD)] [40], mood and physical symptoms [41] and strength of urges to use ST (none/slight/moderate/strong/very strong/extremely strong) [42]. Questions on quitting ST included information on advice to quit in the past 12 months (being asked, and advised health-care provider to quit ST) [39], quit attempt made in the past 12 months (yes/no) [39] and motivation to quit ST (not at all/a little/somewhat/a lot) [43]. Quality of life was assessed using the three-level version of the European Quality of Life 5 Dimensions 5 Level (EQ-5D) scale [44]. Mediators of ST cessation were collected for feasibility assessment. A baseline saliva sample was also collected for cotinine analysis. In Bangladesh and Pakistan, samples were analysed by a specialist laboratory (ABS Laboratories, York, UK), while in India the samples were analysed locally at the Shriram Institute for Industrial Research, New Delhi.

At the 6, 12 and 26-week follow-ups, participants self-reported use of any tobacco product in the previous week and since their quit date. At 26 weeks, participants who self-reported abstinence since the quit date were asked to provide saliva samples for biochemical verification. Information on adverse and serious adverse events was collected using a structured checklist, administered face-to-face or via a telephone call, to assess the frequency and severity of adverse and severe adverse events (SAEs). Details of how adverse events were handled are provided in the published protocol [33].

Outcome measures

The feasibility of the trial was assessed by analysing data on recruitment, randomization and retention, intervention delivery and completeness of data collection.

For recruitment, randomization and retention, we reviewed and analysed study logs for information on (a) recruitment time-lines, (b) the number of participants screened, found eligible, recruited and randomized, (c) characteristics of non-consenting and ineligible participants and (d) retention at trial follow-up (i.e. attendance at 6, 12 and 26 weeks data collection time-points), together with reasons for dropout.

For intervention delivery, we reviewed and analysed data from intervention delivery logs to assess (a) attendance at pre-quit and post-quit sessions (BISCA), (b) the number of participants receiving low- (4 mg) versus high- (6 mg) dose NRT and (c) the number of participants reporting adherence to NRT at follow-up visits.

For the completeness of data collection, we reviewed and analysed data obtained using study questionnaires to assess completion rates of baseline and follow-up assessments in each arm. Study logs were also reviewed to assess the provision of saliva samples at baseline and 26 weeks.

Other measures

Secondary objectives focused on the identification of cessation outcomes. These included abstinence from all forms of tobacco (smoked and smokeless) in the past week at 6-, 12- and 26-week assessments and biochemically verified continuous abstinence at 26 weeks. In line with the Russell standard, biochemically verified abstinence was defined as self-reported abstinence from all forms of tobacco since the quit date and a salivary cotinine concentration < 15 ng/ml [35].

Statistical methods

Sample size

The sample size estimation was conducted using Viechtbauer *et al.*'s [45] approach for pilot studies. Assuming the proportion of feasibility outcomes (loss to follow-up and incomplete data) to lie between 5 and 10%, we estimated at least 60 participants per country (15 per trial arm) using a 95% confidence level. We inflated this to 20 participants per trial arm per country and then further inflated the overall figure by 10% to account for the loss to follow-up. Hence, the total sample size was 264 participants (66 per trial arm).

Statistical analysis

Descriptive data analyses were used to summarize baseline characteristics (as well as EQ-5D-3L scores at 26 weeks) and to report on the feasibility objectives described above. Mean or median (with SD or range) for continuous variables and frequencies (absolute and relative) for categorical variables were used.

We used log-binomial regression to estimate treatment effects and utilized semi-robust standard errors. The models reported in the main manuscript included the interventions, BISCA (any versus none) and NRT (any versus none), and the recruiting site (five in total) as main effects. For these models, we reported the risk ratios (RR) and 95% confidence intervals (CIs). We also reported the estimates of the interaction term between the two interventions as a secondary analysis, as per the approach of Montgomery *et al.* [46]. In the event of no convergence, we attempted to control for the country instead of the site in the first instance. If convergence remained an issue, we reported the estimates based on the model with the effects of the interventions only.

As this was a pilot study, all the treatment effect analyses were exploratory in nature. All those included in the analysis sample were analysed as randomized. All those lost to follow-up were considered tobacco users. For week 26 biochemically verified continuous abstinence, those who were not lost to follow-up but did not provide a salivary sample to assess cotinine concentration or a CO reading were assumed to be tobacco users.

We were not able to control for both the sites and the country in the same model due to the limited number of sites per country, in some cases one site per country. Similarly, the limited number of observations and events per site meant that we were not able to fit three-way interactions between the interventions and the sites. The estimates of the interaction term between the two interventions are also reported for the model that included the three two-way interactions between the two interventions and the sites.

Country-specific estimates for the interventions and the models obtained using a logistic regression approach to estimate the corresponding odds ratios, as well as descriptive analyses of EQ-5D-3L by trial and factorial arms, are presented (Supporting information, Tables S5–S7). All statistical analyses were performed on Stata version 17 [47].

RESULTS

Trial recruitment

Participants were recruited over 12 months starting in Bangladesh in December 2019, in Pakistan in February 2020 and in India in September 2020. In Bangladesh, initial recruitment was affected by slum eviction in the localities served by the study sites. Later, all sites experienced disruption in recruitment due to COVID-19 lockdowns, with activities halted between March and July 2020. As a result of delays caused by COVID-19, 50% of the sample to be recruited in India was allocated to Bangladesh. Overall, 392 individuals who expressed initial interest were screened against the eligibility criteria. A total of 272 (69.3%) were eligible and 264 (97.0%) were recruited: 132 in Bangladesh, 44 in India and 88 in Pakistan (Figure 2: PRISMA flow diagram and Supporting information, Table S1). Non-daily ST use (54.7%), dual tobacco use (17.4%) and not willing to quit in the next 30 days (14.2%) were the most common reasons for exclusion (Supporting information, Table S2).

Participant characteristics

Socio-demographic variables, tobacco-related characteristics and EQ-5D scores were balanced across trial arms (Table 1). Participants were on average 35 years old [standard deviation (SD) = 12.5] and males were slightly over-represented (n = 140, 53%). Just under one-third of participants had no formal education (n = 74, 28.2%). ST use was initiated in early adulthood (mean = 21.6 years, SD = 10.8). The most prevalent ST product consumed in the past week was *Paan* with tobacco (60.6%), followed by *Mawa* (24.2%) and *Gutka* (7.95%). One-third of the participants reported extremely strong (n = 87, 32.9%) urges to use ST, which was consistent with the high Fagerström test scores (mean = 5.3, SD = 1.9) and levels of baseline salivary cotinine (mean = 335.3 ng/dl, SD = 327.4). Approximately half of the participants (n = 129, 48.8%) had made previous quit attempts, mainly on their own (92.2%, data not shown). Among those who had previously visited health-care providers (n = 101), 58 (57.4%) were asked about ST use, the majority of whom were also advised to quit (n = 56, 98.2%).

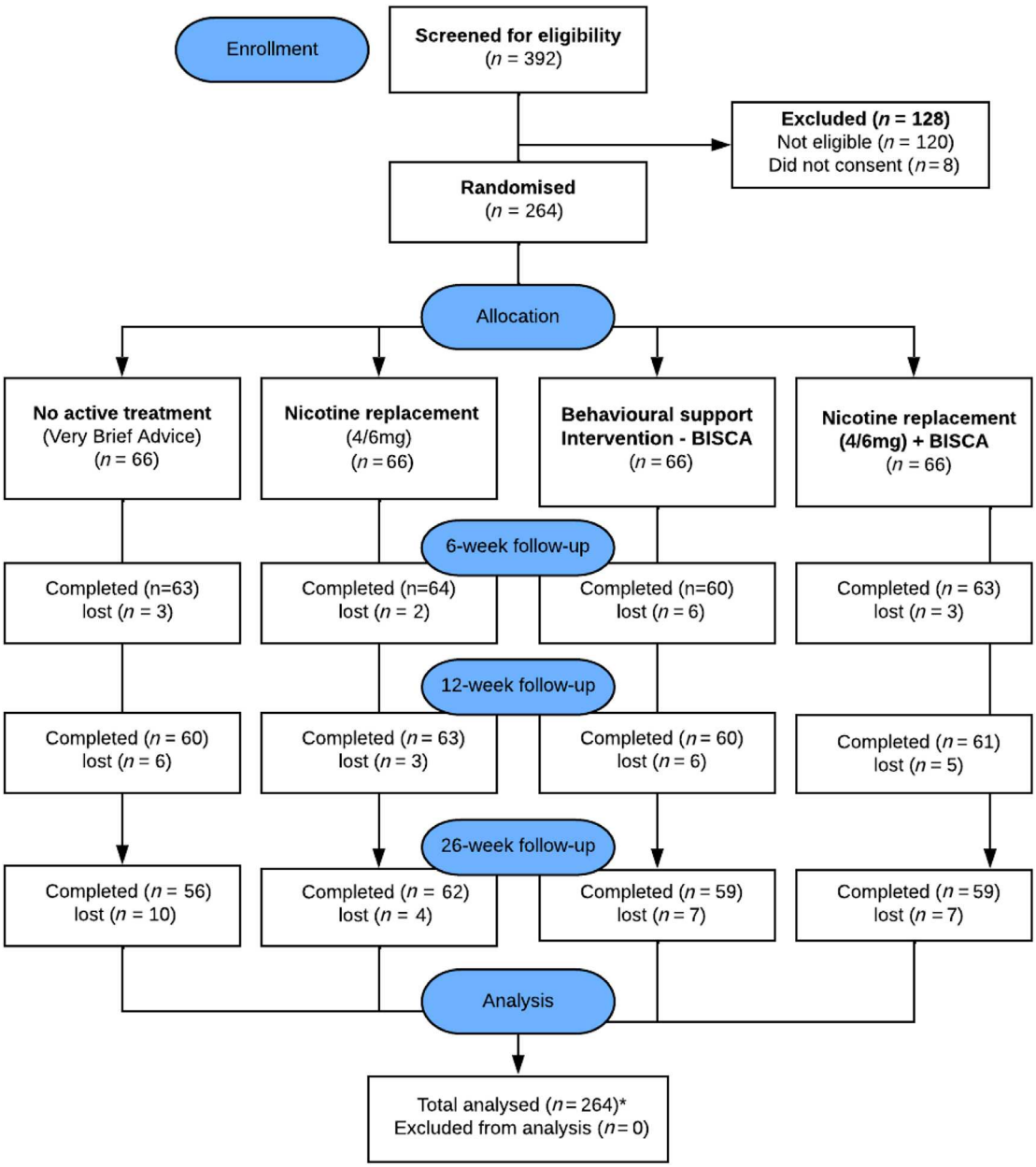

FIGURE 2 Consort diagram providing details of overall recruitment, randomization and retention, presented by multi-arm groups.

Feasibility outcomes

Intervention delivery and retention at follow-up

All participants randomized to BISCA (*n* = 132) received at least one pre-quit session, with 16 (12.1%) receiving two or more pre-quit sessions. Overall, 114 (86.3%) participants attended quit sessions; however, this varied throughout Bangladesh (96.9%), India (86.3%) and Pakistan (70.4%). Eighty-seven participants (65.9%) attended one or more post-quit sessions; attendance was highest in Bangladesh (65; 98.4%, the mean number of post-quit sessions attended = 4.8, SD = 1.6) (Supporting information, Table S3). Of 132 participants receiving NRT, 58 (43.9%) received a 6-mg dose. A higher proportion of participants in India (*n* = 20, 90.9%) reported adherence to NRT, followed by Bangladesh (*n* = 30/66, 45.5%) and Pakistan (*n* = 22/44, 50%) (data not shown).

Retention at 6, 12 and 26 weeks

Most follow-ups were conducted during COVID-19, either remotely or under strict cross-infection control procedures. High retention rates were achieved, with 250 (94.7%), 244 (92.4%) and 236 (89.4%) participants completing follow-ups at 6, 12 and 26 weeks,

TABLE 1 Characteristics of trial participants, overall and stratified by trial arm[a] (n = 264).

Characteristics	Very brief advice (n = 66)	Nicotine replacement (n = 66)	BISCA (n = 66)	Nicotine replacement + BISCA (n = 66)	Total participants (n = 264)
Socio-demographic characteristics					
Age in years mean (SD, range)	35.2 (12.9, 18–75)	34.5 (11.7, 18–75)	36.4 (12.7, 18–70)	33.9 (12.7, 18–70)	35.0 (12.5, 18–75)
Sex (male)	36 (54.5)	39 (59.1)	31(46.9)	34 (51.5)	140 (53.1)
Education					
No education	16 (24.2)	14 (21.2)	19 (28.8)	25 (37.8)	74 (28.2)
Primary	17 (25.7)	11 (16.6)	18 (27.2)	9 (13.6)	55 (20.9)
Middle	13 (19.7)	14 (21.2)	9 (13.6)	6 (9.1)	42 (16.0)
Secondary	11 (16.7)	18 (27.3)	7 (10.6)	10 (15.1)	46 (17.5)
Higher secondary	8 (12.1)	6 (9.1)	7 (10.6)	12 (18.2)	33 (12.6)
Other	1 (1.5)	3 (4.5)	5 (7.5)	3 (4.5)	12 (4.5)
Smokeless tobacco: initiation, current use and dependence					
Age at first ST use mean (SD)	22.4 (12.1)	21.1 (10.1)	22.3 (10.6)	20.6 (10.8)	21.6 (10.9)
Age at first ST use, median (Q25, Q75)	19 (14, 26)	18 (15, 26)	20 (15, 29)	18 (14, 25)	19 (14, 26)
Type of ST products used in past 7 days[b]					
Tobacco Paan	39 (59.1)	41 (62.1)	40 (60.6)	40 (60.6)	160 (60.6)
Mawa	17 (25.7)	14 (21.2)	17 (25.7)	16 (24.2)	64 (24.2)
Gutka	3 (4.5)	8 (12.1)	4 (6.0)	6 (9.1)	21 (7.9)
Khaini	2 (3.0)	4 (6.0)	6 (9.1)	7 (10.6)	19 (7.2)
Paan masala	5 (7.6)	6 (9.1)	5 (7.6)	1 (1.5)	17 (6.4)
Gul	6 (9.1)	4 (6.0)	4 (6.0)	3 (4.5)	17 (6.4)
Zarda	4 (6.0)	1 (1.5)	1 (1.5)	4 (6.0)	10 (3.8)
Naswar	0 (0.0)	1 (1.5)	5 (7.6)	5 (7.6)	11 (4.2)
Fagerström Test for Nicotine Dependence scores mean (SD)	4.9 (1.9)	5.7 (2.0)	5.5 (1.7)	5.10 (1.9)	5.3 (1.9)
Strength of urges to use ST					
None	3 (4.5)	2 (3.0)	0 (0)	1 (1.5)	6 (2.3)
Slight	3 (4.5)	5 (7.6)	7 (10.6)	3 (4.5)	18 (6.8)
Moderate	15 (22.7)	13 (19.7)	13 (19.7)	16 (24.2)	57 (21.6)
Strong	8 (12.1)	7 (10.6)	7 (10.6)	10 (15.1)	32 (12.1)
Very strong	15 (22.7)	17(25.6)	16 (24.2)	16 (24.2)	64 (24.2)
Extremely strong	22 (33.3)	22 (33.3)	23 (34.8)	20 (30.3)	87 (32.9)
Urge to use ST in the past 24 hours					
Not at all	3.0 (4.5)	2.0 (3.0)	0.0 (0.0)	1.0 (1.5)	6.0 (2.3)
A little of the time	6.0 (9.1)	6.0 (9.1)	5.0 (7.6)	2.0 (3.0)	19.0 (7.2)
Some of the time	7.0 (10.6)	7.0 (10.6)	11.0 (16.7)	14.0 (21.2)	39.0 (14.8)
A lot of time	17.0 (25.8)	13.0 (19.7)	14.0 (21.2)	9.0 (13.6)	53.0 (20.1)
Almost all the time	14.0 (21.2)	20.0 (30.3)	17.0 (25.8)	21.0 (31.8)	72.0 (27.3)
All the time	19.0 (28.8)	18.0 (27.3)	19.0 (28.8)	19.0 (28.8)	75.0 (28.4)
Mood and physical symptoms scale (mood total) mean (SD)[c]	12.3 (4.4)	13.2 (4.4)	13.3 (4.3)	12.5 (4.5)	12.8 (4.4)
Salivary cotinine concentration in ng/dl mean (SD)	358.6 (367.8)	336.6 (371.0)	319.1 (280.3)	326.8 (284.7)	335.3 (327.4)
Quitting smokeless tobacco					
Asked by health-care provider about ST use[d]	11 (52.4)	14 (53.8)	17 (58.6)	16 (64.0)	58 (57.4)

(Continues)

TABLE 1 (Continued)

Characteristics	Very brief advice (*n* = 66)	Nicotine replacement (*n* = 66)	BISCA (*n* = 66)	Nicotine replacement + BISCA (*n* = 66)	Total participants (*n* = 264)
Advised by a health-care provider to quit in the past 12 months[e] (*n* = 57)	11 (100)	14 (100)	15 (93.7)	16 (100)	56 (98.2)
Quit attempt in the past 12 months (yes)	32 (48.5)	34 (51.5)	38 (57.5)	25 (37.9)	129 (48.8)
Motivation to quit ST					
Not at all	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
A little	2 (3.0)	1 (1.5)	1 (1.5)	1 (1.5)	5 (1.9)
Somewhat	4 (6.1)	3 (4.5)	3 (4.5)	3 (4.5)	13 (4.9)
A lot	59 (90.7)	62 (93.9)	62 (93.9)	62 (93.9)	245 (93.2)
Quality of life[f]					
EQ-5D-3L[g] mean (SD)	74.3 (19.6)	75.7 (17.7)	72.9 (19.5)	77.7 (19.3)	75.1 (19.0)

Abbreviations: NRT = nicotine replacement therapy; SD = standard deviation; ST = smokeless tobacco; BISCA = behavioural intervention for smokeless tobacco cessation in adults.
[a]Results are presented as *n* (%) unless indicated otherwise.
[b]Each ST product was assessed separately; the *n* (%) is out of the total sample in each column.
[c]Total score of the five items related to mood: depressed, irritable, restless, hungry, and poor concentration. One participant randomized to NRT had two items missing and another randomized to VBA had one item missing were treated as a worst-case scenario, both were from India.
[d]Out of participants who visited a health-care provider in the last 12 months (*n* = 101).
[e]Out of participants who were asked by a health-care provider about ST use (*n* = 57).
[f]The EQ-5D-3L comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels: no problems, some problems, and extreme problems.
[g]One participant randomized to NRT had a missing value.

respectively. Six- and 12-week follow-up rates were comparable across countries, but lower retention was observed at 26 weeks in Pakistan (81.2%) (Supporting information, Table S1). Withdrawals from the trial (*n* = 3) were due to ongoing medical treatment and personal/family wishes. Loss to follow-up was only observed in Bangladesh (*n* = 10) and Pakistan (*n* = 15), due mainly to non-response (*n* = 17), relocation (*n* = 7) or death due to an unrelated cause (*n* = 1). Several adverse events, mild to moderate in severity, were reported (Supporting information, Table S4); these were balanced across trial arms. One SAE (death, unrelated to the intervention) was recorded in Bangladesh.

Data collection

The majority of participants completed baseline questionnaires, with completeness rates exceeding 99% on demographic information, ST use, mediators of ST use and withdrawal symptoms. This rate dropped slightly for ST use [minimum (minutes) = 97.9%] for follow-up weeks 6, 12, and 26. For the Fagerström scale, it dropped to 93 and 89.8% for weeks 12 and 26, respectively. The lowest completion rate was observed in week 26 for the urges questions (88.6%) and the MPSS questions (96%). Completion rates for items related to adverse events exceeded 97.5%. Although 263 (99.6%) participants provided saliva samples at baseline, only 79/126 (62.7%) did so at week 26.

ST cessation outcomes

Overall, 163 (65.2%) participants self-reported abstinence from tobacco products in the past week at the 6-week follow-up, while 147 (55.7%) self-reported abstinence at 12 and 26 weeks. At 26 weeks, 126 (47.4%) self-reported abstinence from all forms of tobacco since the quit date, although only 23 (8.7%) had biochemically verified continuous abstinence. Abstinence rates were generally higher among those receiving an intervention (Table 2). Log-binomial regression estimates indicated preliminary effects for BISCA (compared to no BISCA) at 12 and 26 weeks and for NRT (compared to no NRT) at 6, 12 and 26 weeks when self-reported abstinence was considered, and comparable effect sizes were observed for both treatments (Table 3). Biochemically verified continuous abstinence at 26 weeks indicated a larger effect size for BISCA (RR = 2.32, 95% CI = 1.01–5.37) than NRT (RR = 1.25, 95% CI = 0.59–2.65). For the model that included an interaction term between the interventions, the estimate for the interaction term was −0.10 (95% CI = −1.81, 1.60, *P*-value = 0.90).

DISCUSSION

To our knowledge, this is the first multi-country pilot RCT of tobacco cessation among adult ST users in South Asia. Both genders were represented in the pilot, and despite being highly dependent

TABLE 2 ST cessation outcomes at 6, 12 and 26 weeks, presented by multi-arm groups.

Follow-up	Observed outcome *n*	VBA *n* (%) 66	NRT *n* (%) 66	BISCA *n* (%) 66	BISCA + NRT *n* (%) 66	Total *n* (%) 264
6 weeks	Self-reported abstinence (past 7 days)	32 (48.5)	49 (74.2)	38 (57.6)	44 (66.7)	163 (61.7)
12 weeks	Self-reported abstinence (past 7 days)	25 (37.9)	43 (65.2)	38 (57.6)	41 (62.1)	147 (55.7)
26 weeks	Self-reported abstinence (past 7 days)	24 (36.4)	38 (57.6)	42 (63.6)	43 (65.2)	147 (55.7)
26 weeks	Self-reported abstinence of all forms of tobacco since quit date	20 (30.3)	27 (40.9)	38 (57.6)	41 (62.1)	126 (47.7)
26 weeks	Biochemically verified (since quit date)	3 (4.6)	4 (6.1)	7 (10.6)	9 (13.6)	23 (8.7)

Abbreviations: VBA = very brief advice; BISCA = behavioural intervention for smokeless tobacco cessation in adults; ST = smokeless tobacco; NRT = nicotine replacement therapy.

TABLE 3 Risk ratios (RR) and 95% confidence interval (CI) estimates of self-reported and biochemically-verified tobacco cessation outcomes for BISCA (any versus none) and NRT (any versus none).

BISCA			NRT		
Participants/total sample	**Reported abstinence**	**RR (95% CI)**	**Participants/total sample**	**Reported abstinence**	**RR (95% CI)**
Week 6: self-reported abstinence from tobacco (past 7 days)[a]					
132/264	82/132	0.98 (0.82–1.18)[a]	132/264	93/132	1.33 (1.09–1.62)[a]
Week 12: self-reported abstinence from tobacco (past 7 days)[a]					
132/264	79/132	1.12 (0.90–1.39)[b]	132/264	84/132	1.31 (1.04–1.65)[b]
Week 26: self-reported abstinence from tobacco (past 7 days)[a]					
132/264	85/132	1.37 (1.12–1.68)[c]	132/264	81/132	1.18 (0.98–1.43)[c]
Week 26: biochemically verified, continuous abstinence from tobacco (since quit date)[a]					
132/264	16/132	2.32 (1.01–5.37)[d]	132/264	13/132	1.25 (0.59–2.65)[d]

Abbreviations: BISCA = behavioural intervention for smokeless tobacco cessation in adults; ST = smokeless tobacco; NRT = nicotine replacement therapy.
[a]These are the estimates based on the model that does not account for the site or country as convergence was not achieved. For the model that included an interaction term between the interventions, the estimate for the interaction term was −0.31 [95% confidence interval (CI) = −0.69, 0.06; *P*-value: 0.10]. For the model that included the three sets of interactions between interventions and sites, the estimate for the interaction term between interventions was −0.15 (95% CI = −0.45, 0.14; *P*-value = 0.31). The logistic regression estimates for the model that accounted for the site are provided in Supporting information, Table S6.
[b]These are the estimates based on the model that does not account for the site or country as convergence was not achieved. For the model that included the interaction term between the interventions, the estimate for the interaction term was −0.43 (95% CI = −0.87, 0.00; *P*-value = 0.05). For the model that included the three sets of interactions between interventions and sites, the estimate for the interaction term between interventions was −0.39 (95% CI = −0.76, −0.01; *P*-value = 0.04). The logistic regression estimates for the model that accounted for the site are provided in Supporting information, Table S6.
[c]These are the estimates based on the model that accounted for the site. For the model that included an interaction term between the interventions, the estimate for the interaction term was −0.41 (95% CI = −0.85, 0.02; *P*-value = 0.06). For the model that included the three sets of interactions between interventions and sites, the estimate for the interaction term between interventions was −0.35 (95% CI = −0.77, 0.06; *P*-value = 0.09).
[d]These are the estimates based on the model that accounted for the site. For the model that included an interaction term between the interventions, the estimate for the interaction term was −0.10 (95% CI = −1.81, 1.60; *P*-value = 0.90). For the model that included the three sets of interactions between interventions and sites, the estimate for the interaction term between interventions was 0.27 (95% CI = −1.66, 2.19; *P*-value = 0.79].

were willing to quit ST. The trial retained almost 90% of participants over 6 months, despite disruption due to COVID-19.

Treatment adherence showed mixed results. The BISCA sessions delivered before and on the quit date were generally well-attended (100 and 86.3%, respectively) compared to post-quit sessions (65.9%). Participants in Bangladesh attended more sessions than those in India and Pakistan throughout the programme. Conversely, adherence to NRT was better in India. Reasons for the drop-off post-quit and country differences in attendance/adherence are being explored together with change in hypothesized mediators in an embedded process evaluation, to be published separately.

Our trial was a pilot study, therefore no definitive conclusions can be drawn regarding intervention efficacy. However, we observed some important trends. Participants who received BISCA or NRT were generally more likely to quit tobacco than those who did not. This was evident for both self-reported (except for BISCA at 6 weeks) and biochemically verified outcomes. Cotinine assessment provided some evidence to suggest that those who quit did not switch to using other tobacco types, although not all participants indicating long-term abstinence provided a saliva sample.

This pilot trial conducted in South Asia was among the first to test NRT and behavioural support among exclusive ST users. Our findings

are consistent with ST cessation trials conducted in Europe and the United States, as well as those summarized in the relevant Cochrane review [24]. Behavioural support has strong potential in South Asia for tobacco cessation efforts [28, 48]. In countries where tobacco-related harms are not widely recognized, behavioural support can increase motivation to quit and provide support to make quit attempts more successful [49]. The adaptation of behavioural support to cultural contexts could further enhance its effect by providing advice on coping strategies, rewarding continued abstinence and seeking social support [29]. Our findings also contribute to the NRT data on ST cessation. Although some non-RCT evidence suggests that NRT is likely to be effective in achieving short-term abstinence for South Asian ST users [50], confidence in its efficacy remains limited, and this needs to be explored further in a larger trial [24].

Our study had several strengths. It was conducted in three countries with a high ST burden. The factorial design allowed us to test two factors and their interactions with fewer experimental runs than in a traditional parallel arm trial. Our recruitment strategy resulted in a balanced participation of men and women from under-represented social strata who were highly dependent upon nicotine. We observed high levels of interest among participants, as evidenced by the high retention rates. Cotinine measurements allowed us to verify our abstinence outcomes biochemically, as well as confirm that those who reported quitting had not substituted smoking for ST. Russell Standard cut-offs (< 15 ng/ml) were used to identify biochemically verified abstinence. The assessment period provided a sufficient 'washout' period for participants taking NRT, which was only provided for an 8-week duration following the quit date. Moreover, given its high cost and limited availability, NRT is unlikely to have been purchased by participants themselves during or after the intervention period.

Our study also had several limitations. We used NRT based on preliminary evidence to suggest its benefit alongside behavioural support. Other widely tested pharmacological products, such as varenicline, could have been useful in ST cessation but were ruled out due to non-uniform availability across the region. We excluded non-daily users and dual users from participation, which limits the generalizability of our findings to the general population of ST users. Variability in session attendance between study sites meant that some participants randomized to the BISCA elements received more frequent behavioural support than others. A limited number of saliva samples could be collected for 26-week biochemical verification. Among possible reasons, one could be follow-up assessments being conducted over the telephone, and another could be participant reluctance to provide samples due to COVID-19. Finally, the feasibility of assessing abstinence beyond 6 months (26 weeks) remains unexplored.

Our pilot trial provides a strong foundation for conducting a definitive trial using a factorial design, which will allow for testing multiple interventions efficiently. A multi-country trial is preferable to extend its generalizability, and our pilot trial has shown that this is feasible. The science of smoking cessation has progressed beyond NRT and behavioural support, with several other pharmacological interventions (e.g. cytisine) [51] and novel nicotine products (e.g. e-cigarettes) being tested for smoking cessation [52]. The evidence on ST cessation is lagging, widening the knowledge and consequently the health gap for ST users of South Asian origin. Given the high prevalence of ST use, ST cessation is a high-priority area for tobacco control efforts, and there is an urgent need for definitive trials with long-term follow-ups in the future.

AUTHOR CONTRIBUTIONS

Faraz Siddiqui: Methodology (equal); project administration (equal); supervision (equal); writing—original draft (lead); writing—review and editing (lead). **Mona Kanaan:** Formal analysis (equal); methodology (equal); project administration (equal); software (equal); supervision (equal); validation (equal); writing—original draft (equal). **Ray Croucher:** Conceptualization (equal); methodology (equal); supervision (equal); writing—original draft (equal); writing—review and editing (equal). **Linda Bauld:** Conceptualization (equal); methodology (equal); project administration (equal); supervision (equal); writing—review and editing (equal). **Fariza Fieroze:** Project administration (equal); resources (equal); supervision (equal); writing—review and editing (equal). **Prashant Kumar Singh:** Project administration (equal); supervision (equal); writing—review and editing (equal). **Laraib Mazhar:** Project administration (equal); supervision (equal); writing—review and editing (equal). **Varsha Pandey:** Project administration (equal); writing—review and editing (equal). **Cath Jackson:** Investigation (equal); methodology (equal); supervision (equal); writing—review and editing (equal). **Rumana Huque:** Project administration (equal); resources (equal); supervision (equal); writing—review and editing (equal). **Romaina Iqbal:** Project administration (equal); resources (equal); supervision (equal); writing—review and editing (equal). **Kamran Siddiqi:** Conceptualization (lead); funding acquisition (lead); methodology (equal); writing—original draft (equal); writing—review and editing (equal).

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DECLARATIONS OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CLINICAL TRIAL REGISTRATION

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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