CLASS-III
Children Learning About Second-hand Smoke: A cluster-randomised controlled trial (ISRCTN28878365)
Statistical Analysis Plan

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1. Background and rationale

Second-hand smoke (SHS) exposure costs 800,000 lives a year [Oberg, 2011]. Children in developing countries are worst affected as smoke-free laws are only partially implemented and private homes and cars remain a key source of SHS exposure [Oberg, 2011]. Currently firm conclusions cannot be drawn from the available evidence on the effectiveness of non-legislative interventions designed to protect children from SHS exposure. Following the success of two feasibility studies [Huque 2015; Siddiqi, 2010] and a pilot trial [Siddiqi, 2019], we plan to evaluate a school-based approach to protect children from SHS exposure in Bangladesh and Pakistan - countries with a strong commitment to smoke-free environments but with high levels of SHS exposure in children.

The CLASS-III trial aims to assess the effectiveness and cost-effectiveness of a school-based Smoke-Free Intervention (SFI) in reducing children's exposure to SHS and consequent reductions in the frequency and severity of respiratory symptoms. SFI is a behavioural intervention that consists of two 45-minute sessions delivered by schoolteachers over two consecutive days in classroom settings. Each session includes classroom presentations, quiz, interactive games, storytelling and role-play. In our feasibility work, these activities helped children learn negotiation skills and develop confidence in persuading their parents/carers to implement smoking restrictions within homes.

We will conduct a two-arm cluster randomised controlled-trial with embedded process and economic evaluations in Dhaka and Karachi. We will recruit and randomise 68 schools (2,720 children), half of the schools will be allocated to the intervention arm receiving SFI and the other half usual education. Salivary cotinine - a highly sensitive and specific biomarker of SHS exposure - at three months post-randomisation is the primary outcome. Secondary outcomes include frequency and severity of respiratory symptoms, school absenteeism and academic performance, smoking behaviour and uptake and quality of life.

2. Trial objectives

Our overall aim is to prevent respiratory and other smoking-related illnesses in low- and middle-income countries (LMIC) by reducing children's exposure to second-hand smoke (SHS). The objectives of the CLASS-III trial are to investigate the effectiveness of a Smoke-Free Intervention (SFI) delivered in schools, with respect to the following outcomes;

(a) Participating children's exposure to second-hand smoke as measured by salivary cotinine concentration at three months post randomisation (primary outcome)
(b) Participating children’s frequency and severity of respiratory symptoms
(c) Smoking behaviour and uptake
(d) School absenteeism and academic performance
(e) General health related quality of life

The embedded process evaluation will investigate;

(f) The implementation of the intervention and barriers/facilitators to implementation
(g) The mechanisms through which the intervention induces change in behaviour
(h) Contextual factors that influence the implementation and effectiveness of the intervention

This document details both the planned analyses undertaken to investigate the effectiveness of SFI with respect to outcomes (a) – (e), and the analyses undertaken to answer the implementation and process evaluation objectives (f) – (g).

3. Design

CLASS-III is a two-arm cluster-randomised controlled trial, with embedded process and economic evaluations, conducted in eligible and consenting primary schools in Bangladesh and Pakistan. Following recruitment of school clusters, and baseline data collection for eligible and consenting (parental consent) year 5 children within these clusters, schools will be randomised in a 1:1 ratio to either the intervention condition (SFI) or control condition (usual education). For schools allocated to the intervention group, the SFI will be delivered to children in participating year 5 classes by their teachers in the classroom setting. Participating children will then be followed up at 3, 6 and 12 months post-randomisation. The primary outcome is salivary cotinine concentration at 3 months post-randomisation. Secondary outcomes include; participant reported frequency and severity of respiratory symptoms, participant reported smoking restrictions at home, participant reported attitude toward smoking and intention to start smoking, teacher reported school absenteeism and academic performance, participant reported general health related quality of life and participant reported health service use.

Schools will be recruited in approximately equal proportion from Bangladesh and Pakistan. A school is eligible to participate if they meet the following eligibility criteria;

- Follows the relevant national curricula
- Uses Bangla, Urdu or Sindhi as their education medium
- Has at least 25 children attending year 5 classes (children aged 9-12 years)
- Does not have only primary school classes
- Has and abides by smoke free policies
- Has not already received SFI training in a previous project

Year five children at participating schools will be eligible for participation if they meet the following eligibility criteria;

- Is not a self-reported tobacco user (smoked or smokeless)
- Does not have a serious condition that is life threatening or requires regular hospitalisation
- Does not have a known history of domestic violence or abuse (in any form)

All children within participating classes will be included within classroom based activities, but children who are ineligible for the trial (according to the criteria above) will not have any intervention materials sent to their homes. Participants with baseline cotinine concentration outside of the range [0.1, 12]ng/mL will be excluded from the primary analysis[1], as these children (i.e. those not exposed to second hand smoke and those actively smoking) are not the intended target of the intervention [Jarvis, 2008]. However, outcome data will be collected from these participants (due to practical difficulties of excluding these participants from follow up data collection on the basis of their baseline cotinine

[1] Here [a, b] denotes the set of real numbers x such that $a \leq x \leq b$

concentration measurement), and these data will be included in the various planned secondary analyses. For further details on the design and implementation of study interventions and procedures, see https://www.isrctn.com/ISRCTN28878365.

4. Randomisation

Once baseline data are collected, participating schools will be randomly allocated (1:1) to the two trial arms (approximately 34 in each arm) using minimisation. The minimisation will be used to balance treatment allocation on country (Bangladesh or Pakistan), school type (Public or Private), ratio of boys to girls (B:G) in year five (B:G < 0.95, 0.95 ≤ B:G ≤ 1.05, B:G > 1.05) and the number (N) of students in year five at the participating school cluster (N < 30, 30 ≤ N ≤ 60, N > 60). The first cluster will be allocated using simple randomisation, with minimisation used to allocate all subsequent clusters. The minimisation will be implemented using the user written Stata command `rct_minim` [Ryan, 2009]. Because of the nature of the intervention, it will not be possible to mask the children and schoolteachers from the allocation. To avoid recruitment bias, we will ensure that all baseline data are collected before cluster treatment allocation. In addition, we will not reveal the allocation status of the schools to our field data collectors. However, we recognise that once they are out in the field and speak to teachers and children, total concealment may not be possible. Given that our primary outcome relies on an objective measure (salivary cotinine), we perceive this to be a low risk to the validity of our findings.

5. Sample size

Informed by the results of the CLASS-II trial [Siddiqi, 2019], we assume an average cluster size of 40, that 5% of children within a given cluster are not eligible (i.e. they have a salivary cotinine concentration less than 0.1ng/mL or greater than 12 ng/mL, report tobacco use or have a history of domestic abuse) and that 10% of children who are eligible (within cluster) do not provide a salivary cotinine reading at 3 months post-randomisation. Under these assumptions, we would expect to obtain (on average) primary outcome data for 34.2 participants per cluster. Rounding this figure up to 35, and assuming a coefficient of variation in cluster size (at follow-up) of 0.4 and intra-cluster correlation of 0.05 (based approximately on the data collected in the CLASS-II pilot trial), gives a design effect of 2.98. Assuming the marginal variance of the primary outcome is 1.38^2, a total of 766 participants would be required for an individually randomised trial to obtain 80% power to detect a difference in salivary cotinine concentration of 0.28 ng/mL in a two-sided t-test (H_0: $\delta = 0$ against H_1: $\delta \neq 0$) of size 5%. Hence approximately 2284 primary endpoints (i.e. valid salivary cotinine measurements at 3 months post-randomisation) are required to obtain 80% power for the cluster randomised design. Assuming 34 observations per cluster, approximately 2284/34 ≈ 67.2 clusters are required, hence the total recruitment target of 68 clusters (2720 children).

6. Outcomes

6.1. Primary outcome

Because of its very short half-life (2 hours), nicotine is not recommended as a measure of tobacco exposure. On the other hand, cotinine–the major proximate metabolite of nicotine–has a relatively long half-life (17 hours), which allows detection of tobacco exposure even after three days. Therefore the primary outcome for the CLASS-III trial is salivary cotinine concentration (ng/mL) measured at 3 months post-randomisation. Saliva samples will be sought for all participating children at baseline and three months post-randomisation.

6.2. Secondary outcomes

6.2.1. Respiratory and aural symptoms

During the four weeks prior to each follow up (3, 6 and 12 months post-randomisation), participating children will be asked to keep a diary (completed daily) documenting the frequency that they have experienced six upper respiratory tract symptoms, seven lower respiratory tract symptoms and three aural symptoms (see Table 1a for details), and the severity of these. For each day (at each time point), participating children will be asked to indicate the extent they have suffered with each of the 16 symptoms according to a four level ordinal scale; 0 = Symptom free, 1 = Mild symptoms, 2 = Severe symptoms, 3 = Very severe symptoms. These data will be used to generate three daily summary scores; the (daily) upper respiratory tract score (0 – 18 or missing), lower respiratory tract score (0 – 21 or missing) and aural score (0 – 9 or missing). These daily summary scores will be obtained by summing the responses to the relevant symptoms (see Table 1) for each day. Prior to summation, missing values for a specific symptom (e.g. cough on waking) on a specific day (e.g. day 5) will be imputed with the median of the observed scores for that symptom on any adjacent days (e.g. days 4 and/or 6). Then, if <33.3% of the responses for a given scale (e.g. Lower respiratory tract), for a given participant on a given day are missing, the missing scores will be imputed with the median of the relevant non-missing scores (for that participant on that day). If ≥33.3% of the responses for a given scale, for a given participant on a given day are missing, then the summary score (e.g. upper respiratory tract score) for that day will be treated as missing. If any of the symptoms in a given scale are still missing following these two imputation steps, then the daily summary score (for that participant, for that day) will be considered missing. Missing daily summary scores (e.g. lower respiratory tract score on day 5) will be imputed with the median of the observed summary scores for that scale on any adjacent days (e.g. lower respiratory tract scores on days 4 and/or 6) if these scores are available.

Table 1: Details of symptoms data collected. Each symptom is scored 0, 1, 2 or 3 on each day for 28 days prior to each of the three follow up time points

Type	Symptom
Upper respiratory tract	1. Runny nose and/or sneezing 2. Blocked and/or stuffy nose 3. Sore throat and/or hoarse voice 4. Headaches and/or face aches 5. Aches and/or pains elsewhere 6. Chill/fever and/or shivers
Lower respiratory tract	7. Cough on waking 8. Wheeze on waking 9. Cough during the day 10. Wheeze during the day

	11. Shortness of breath during the day 12. Night cough 13. Wheeze or shortness of breath during the night
Aural	14. Hearing loss 15. Drainage from your ear 16. Pain in your ear

6.2.2. Second Hand Smoke exposure

Participants will be asked about various aspects of their potential exposure to second hand smoke, both within the home and outside the home. These questions will be asked at baseline (prior to randomisation), and at 3, 6, and 12 months post-randomisation.

6.2.2.1 Prevalence of smoking within home

At each time point, participating children will be asked whether anybody who lives with them smokes tobacco. Participants who indicate that they do live with somebody who smokes tobacco, will be asked how many adults (≥18 years of age) and children (<18 years of age) in the household smoke. Participants will also be asked whether people who visit their home smoke and whether anybody who lives with them uses an e-cigarette.

6.2.2.2 Smoking restrictions and visibility within home

At each time point, participants who indicate that they do live with somebody who smokes tobacco, will be asked to indicate where the people who live with them smoke; 1) Anywhere inside the home, 2) In some rooms inside the home, 3) Only in one room inside the home, 4) Only outside. All participants will also be asked to report where in the home any visitors smoke (regardless of the smoking status of residents), using the same list of options. Responses to these questions will be used to generate a four category variable indicating the presence and extent of any smoking restrictions within the home (see Table 2a for details). Participants will also be asked to indicate whether any residents smoke in front of children (Yes/No), and whether any visitors smoke in front of children (Yes/No). Responses will be used to generate a three level categorical variable indicating the visibility of smoking within the home (see Table 2b for details).

Table 2a: Smoking restrictions

Residents smoke?	**Visitors smoke?**	**Category**	**Definition**
Yes	Yes	Complete restrictions No restrictions Partial restrictions	Residents and visitors only smoke outside Residents or visitors smoke anywhere in the home Otherwise
Yes	No	Complete restrictions No restrictions Partial restrictions	Residents only smoke outside Residents smoke anywhere in the home Otherwise
No	Yes	Complete restrictions No restrictions Partial restrictions	Visitors only smoke outside Visitors smoke anywhere in the home Otherwise
No	No	No smoking within home	-

Table 2b: Smoking visibility

Residents smoke?	**Visitors smoke?**	**Category**	**Definition**
Yes	Yes	Smoking not visible	Residents and visitors do not smoke in front of children

		Smoking visible	Residents or visitors smoke in front of children
Yes	No	Smoking not visible Smoking visible	Residents do not smoke in front of children Residents smoke in front of children
No	Yes	Smoking not visible Smoking visible	Visitors do not smoke in front of children Visitors smoke in front of children
No	No	No smoking within home	-

6.2.2.3 Second hand smoke exposure outside of home

At each time point, participants will be asked to report any second hand tobacco smoke exposure that may have occurred outside of the home in the previous seven days. In particular participants will report whether they have been in a vehicle with somebody smoking (Yes/No), and whether they have been near somebody smoking in another location; Mosque, Market, School or university, Playground or recreational area, Bus/rickshaw stand, Tea stall, Other. Responses to these questions will be analysed and reported as standalone items (i.e. will not be combined into any sort of composite score).

6.2.3. Smoking related behaviour

At baseline (prior to randomisation) and at 3, 6 and 12 months post-randomisation, participants will be asked various questions about their use of tobacco and/or their susceptibility toward starting smoking.

6.2.3.1 Tobacco smoking behaviour and intentions

Participants' Yes/No responses to "Have you ever tried or experimented with tobacco smoking, even a few puffs?" and "Do you smoke tobacco regularly or frequently?" will be used to derive three categories (at each time point); Frequent or regular smoker (1), Tried, but not a frequent or regular smoker (2), Not tried (3).

Participants that are in categories (1) or (2) (i.e. Frequent or regular smokers or experimenters) are asked about the number of days they have smoked in the last 30 days, and the number of cigarettes, bidis and sessions of shisha/hookah in their lifetime. Participants in category (3) (i.e. not tried tobacco smoking) will be asked for a Yes/No response to "Do you think that you will try tobacco smoking soon?", and participants that are in categories (2) or (3) will be asked "If one of your best friends were to offer you to smoke tobacco, would you smoke it?" and "Do you think you will be smoking tobacco 1 year from now?". Both of these questions have four levels of response; Definitely yes, Probably yes, Probably not, Definitely not.

Details of this series of questions are given in Table 3a. Participants' responses to these questions will be used to derive scores for a five point smoking uptake scale (see Table 3b for details) [Pierce, 1995].

Table 3a: Tobacco smoking behaviour and intentions questions

Variable name and validation	Question	Response
crf_smk_q19	Have you tried or experimented with tobacco smoking even a few puffs?	Yes (1) No (0)
crf_smk_q20 (variable shown if and only if crf_smk_q19 = "Yes")	Do you smoke tobacco regularly or frequently?	Yes (1) No (0)

crf_smk_q21 (variable shown if and only if crf_smk_q19 = “Yes”)	Think about the last 30 days. On how many of these days did you smoke?	Integer (Min = 0, Max = 30)
crf_smk_q22 (variable shown if and only if crf_smk_q19 = “Yes”)	Over your whole life which of the following tobacco products have you smoked? (select all that apply)	Cigarettes (crf_smk_q22(1)) Bidis (crf_smk_q22(2)) Shisha/Hookah (crf_smk_q22(3))
crf_smk_q22cig (variable shown if and only if crf_smk_q22(1) = 1)	How many cigarettes?	Integer (Min = 0, Max = 1000)
crf_smk_q22bidi (variable shown if and only if crf_smk_q22(2) = 1)	How many bidis?	Integer (Min = 0, Max = 1000)
crf_smk_q22shi (variable shown if and only if crf_smk_q22(3) = 1)	How many sessions of shisha/hookah?	Integer (Min = 0, Max = 1000)
crf_smk_q23 (variable shown if and only if crf_smk_q19 = “No”)	Do you think you will try tobacco smoking soon?	Yes (1) No (0)
crf_smk_q24 (variable shown if and only if crf_smk_q19 = “No” or crf_smk_q20 = “No”)	If one of your best friends were to offer you to smoke tobacco, would you smoke it?	Definitely not (0) Probably not (1) Probably yes (2) Definitely yes (3)
crf_smk_q25 (variable shown if and only if crf_smk_q19 = “No” or crf_smk_q20 = “No”)	Do you think you will be smoking tobacco one year from now?	Definitely not (0) Probably not (1) Probably yes (2) Definitely yes (3)

Table 3b: Smoking uptake scale

Level	Definition
Non-susceptible non-smokers	Never tried or experimented with tobacco (3) and does not think they will try tobacco smoking soon, and would definitely not smoke tobacco if offered it by a friend, and definitely thinks they will not be smoking 1 year in the future crf_smk_q19 = “No” & crf_smk_q23 = “No” & crf_smk_q24 = “Definitely not” & crf_smk_q25 = “Definitely not”
Susceptible non-smokers	Never tried or experimented with tobacco (3) and thinks that they will try tobacco smoking soon, or would not "definitely not” smoke tobacco if offered it by a friend, or does not think they will “definitely not” be smoking 1 year in the future crf_smk_q19 = “No” & (crf_smk_q23 = “Yes” or crf_smk_q24 ≠ “Definitely not” or crf_smk_q24 ≠ “Definitely not”)
Early experimenters	Has tried or experimented with tobacco and has smoked fewer than 5 cigarettes in lifetime and has smoked fewer than 5 bidis in lifetime and has had fewer than 5 session of shisha/hookah in lifetime crf_smk_q19 = “Yes” & crf_smk_q20 = “No” & crf_smk_q22cig < 5 & crf_smk_q22bidi < 5 & crf_smk_q22shi < 5
Advanced experimenters	Has tried or experimented with tobacco and has smoked more than 5 cigarettes in lifetime or has smoked more than 5 bidis in lifetime or has had more than 5 session of shisha/hookah in lifetime crf_smk_q19 = “Yes” & crf_smk_q20 = “No” & (crf_smk_q22cig ≥ 5 or crf_smk_q22bidi ≥ 5 or crf_smk_q22shi ≥ 5)
Established smokers	Has tried or experimented with tobacco and does smoke regularly/frequently crf_smk_q19 = “Yes” &

	crf_smk_q20 = “Yes”

6.2.3.2 Smokeless tobacco behaviour and intentions

At each time point participants will be asked whether they have tried or experimented with smokeless tobacco (e.g. Betel leaf, Jarda, Guthka, Gul etc.). Participants who indicate that they have never tried or experimented with smokeless tobacco will be asked whether they think they will try smokeless tobacco soon. Participants that report some previous smokeless tobacco use will be asked about their use of smokeless tobacco is the past 30 days and past 7 days. All participants will be asked whether they would use smokeless tobacco if offered it by a friend and whether they think they will be using smokeless tobacco one year in the future. Both of these questions have four levels of response; Definitely yes, Probably yes, Probably not, Definitely not.

6.2.4. EQ-5D-5Y

Health related quality of life will be measured at baseline and all three follow up time points using the EQ-5D-5Y [EuroQoL Research Foundation, 2020].

6.2.5. Absenteeism and academic performance

Participating schools will be asked to provide a report on the academic performance of participating children at baseline and all follow up time points, and a record of the number of days missed each month between follow ups.

6.2.5.1 Absenteeism

At each time point, schools will be asked to provide a record of the number of days of school participating children missed since the previous follow up (in the previous month at baseline). These data will be used to derive the cumulative number of school days missed (since baseline) at each follow up time point.

6.2.5.2 Academic Performance Questionnaire

At baseline and each follow up time point, schools will be asked to report the academic performance of participating children using the Academic Performance Questionnaire (APQ). The APQ will be completed by participating children’s class teachers, and is comprised of 10 items with responses given using either four or five point ordinal scales (see Table 4 for details).

Table 4: Academic Performance Questionnaire

1	Compared with the average students in your class, how well is this child able to read orally?	Well above average At or somewhat above average Somewhat below average Well below average
2	Compared with the average students in your class, how well is this child able to comprehend what they read?	Well above average At or somewhat above average Somewhat below average Well below average
3	Compared with the average students in your class, how well is this child able to perform math calculations?	Well above average At or somewhat above average Somewhat below average Well below average
4	Compared with the average students in your class, how well is this child able to perform math word problems?	Well above average At or somewhat above average Somewhat below average

		Well below average
5	Compared with the average students in your class, how well is the child able to write short stories or essays?	Well above average At or somewhat above average Somewhat below average Well below average
6	Please estimate the percentage of written math work completed (regardless of accuracy) relative to classmates.	90% to 100% 80% to 89% 70% to 79% 60% to 69% 0% to 59%
7	Please estimate the accuracy of completed written math work	90% to 100% 80% to 89% 70% to 79% 60% to 69% 0% to 59%
8	Please estimate the percentage of written language/arts work completed (regardless of accuracy) relative to classmates.	90% to 100% 80% to 89% 70% to 79% 60% to 69% 0% to 59%
9	Please estimate the accuracy of completed written language/arts work	90% to 100% 80% to 89% 70% to 79% 60% to 69% 0% to 59%
10	Please estimate the percentage of homework completed	90% to 100% 80% to 89% 70% to 79% 60% to 69% 0% to 59%

6.2.6. Process evaluation

A mixed-methods process evaluation will explore three key functions: mechanisms of impact, context and implementation. Quantitative data will be collected in a short questionnaire completed by participants at all time points.

6.2.6.1 Mediators

At each time point all participants will complete questions assessing mediators of behaviour change. These are based upon the evidence for the links between the behaviour change techniques [Michie, 2014] that constitute the active ingredients of the intervention, and the respective mechanisms of actions [Michie, 2018] of those techniques. Response options for six risk awareness questions are true, false or don't know. Response options for eight questions measuring outcome expectancies, self-efficacy, intentions, and action planning are strongly disagree, disagree, not sure, agree, strongly disagree.

6.2.6.2 Intervention engagement and acceptability

At 3-months follow-up, participants in the intervention group will complete one question assessing their engagement with the intervention: "Have you taken part in any smoke-free intervention activities with your class?" with response items yes or no. Eight questions will explore acceptability of the eight intervention activities, using response items of really dislike, dislike, neither, like, really like. One question asks the children to tick the three most useful activities.

6.2.6.3 Fidelity of intervention delivery

Fidelity checks of intervention delivery will be conducted in one third of the schools allocated to the intervention in each country (5-6 per country). These schools will be randomly selected without any constraints placed on this selection (i.e. no stratification or weighting etc.). All six intervention sessions will be assessed using the fidelity index. All session components are scored from not implemented, partially implemented, fully implemented. The number of session components are as follows: session 1A – 18, 1B - 2, session 2 - 1, session 3 - 2, session 4 -1, session 5 - 2, session 6 -2.

6.3. Data Collection and Follow-up

Data will be collected from participating school clusters and/or teachers and children within these participating clusters at five time points; during screening (school level data only), at baseline (just prior to randomisation) and at 3, 6 and 12 months post-randomisation.

6.3.1. Cluster level data

- Country (Bangladesh or Pakistan)
- Number of boys/girls in Y5 at participating cluster
- School status (Public or Private)
- School level (Only primary, Only secondary, Both primary and secondary)
- Y5 teachers' ages (years)
- Y5 teachers' genders (Male or Female)
- Y5 teachers' highest qualifications (Honours degree, Master's degree, PhD, Teaching diploma, Other)
- Y5 teachers' years of teaching experience
- Y5 teachers' smoking statuses
- Eligibility criteria (see Section 3)
- Date screened
- Date approached for consent
- Cluster consent information
- Date recruitment commenced
- Date of randomisation
- Date of training
- Date intervention started/completed
- Follow-up visit dates
- Cluster level withdrawals and/or loss to follow-up

6.3.2. Baseline data (participant level)

- Date of birth
- Sex (Male or Female)
- Outside space at home (Yes or No)
- Number of bedrooms in home
- Household amenities (Electricity, Flush toilet, Fixed telephone, Cell telephone, Television, Radio, Refrigerator, Car, Moped/Scooter/Motorcycle)
- Number of adults (≥18 years) living with participant
- Number of adults (≥18 years) that smoke
- Number of children (<18 years) living with participant
- Number of children (<18 years) that smoke
- Where do residents smoke (Anywhere in home, In some rooms in home, Only in one room, Only outside)
- Do residents smoke in front of children (Yes or No)
- Do people who visit the home smoke (Yes or No)
- Where do visitors smoke (Anywhere in home, In some rooms in home, Only in one room, Only outside)
- Do visitors smoke in front of children (Yes or No)
- Second hand smoke exposure in vehicles (Yes or No)

- Second hand smoke exposure elsewhere (Mosque, Market/Mall/Bazar, School/University, Playground, Bus stand/Three wheeler CNG stand/Rickshaw stand, Tea stall, Other)
- Number of shops selling cigarettes or tobacco within five minutes walking distance of home
- Number of shops selling cigarettes or tobacco within five minutes walking distance of school
- Do residents use e-cigarettes (Yes or No)
- Has participant ever tried or experimented with tobacco (Yes or No)
- Does participant smoke regularly or frequently (Yes or No)
- Number of smoking days in last 30 days
- Number of cigarettes smoked in lifetime
- Number of bidis smoked in lifetime
- Number of shisha/hookah session in lifetime
- Intention to try tobacco smoking soon (Yes or No)
- Would participant smoke tobacco if offered it (Definitely yes, Probably yes, Probably not, Definitely not)
- Does participant think they will be smoking one year in future (Definitely yes, Probably yes, Probably not, Definitely not)
- Has participant ever tried or experimented with smokeless tobacco (Yes or No)
- Intention to try smokeless tobacco soon (Yes or No)
- Would participant use smokeless tobacco if offered it (Definitely yes, Probably yes, Probably not, Definitely not)
- Does participant think they will be using smokeless tobacco one year in future (Definitely yes, Probably yes, Probably not, Definitely not)
- Respiratory symptoms in previous week (Wheeze on waking, Cough during day, Shortness of breath during day, Night cough, wheeze or shortness of breath during night, Runny nose or sneezing, Blocked or stuffy nose, Sore throat or hoarse voice, Headaches/face aches, Aches/pains elsewhere, Chill/shivers)
- Using medication (Yes or No)
- Reason for medication use (Asthma, Other respiratory illness, Other health condition)
- EQ-5D-Y
- Mediator questions
- Academic performance questionnaire (teacher completed)
- Number of days absent in month prior to baseline data collection
- Salivary cotinine concentration measurement (ng/mL)

6.3.3. Three month follow up (participant level)

- Outside space at home (Yes or No)
- Number of bedrooms in home
- Number of adults (≥18 years) living with participant
- Number of adults (≥18 years) that smoke
- Number of children (<18 years) living with participant
- Number of children (<18 years) that smoke
- Where do residents smoke (Anywhere in home, In some rooms in home, Only in one room, Only outside)
- Do residents smoke in front of children (Yes or No)
- Do people who visit the home smoke (Yes or No)
- Where do visitors smoke (Anywhere in home, In some rooms in home, Only in one room, Only outside)
- Do visitors smoke in front of children (Yes or No)
- Second hand smoke exposure in vehicles (Yes or No)
- Second hand smoke exposure elsewhere (Mosque, Market/Mall/Bazar, School/University, Playground, Bus stand/Three wheeler CNG stand/Rickshaw stand, Tea stall, Other)
- Number of shops selling cigarettes or tobacco within five minutes walking distance of home
- Number of shops selling cigarettes or tobacco within five minutes walking distance of school
- Do residents use e-cigarettes (Yes or No)
- Has participant ever tried or experimented with tobacco (Yes or No)
- Does participant smoke regularly or frequently (Yes or No)
- Number of smoking days in last 30 days

- Number of cigarettes smoked in lifetime
- Number of bidis smoked in lifetime
- Number of shisha/hookah session in lifetime
- Intention to try tobacco smoking soon (Yes or No)
- Would participant smoke tobacco if offered it (Definitely yes, Probably yes, Probably not, Definitely not)
- Does participant think they will be smoking one year in future (Definitely yes, Probably yes, Probably not, Definitely not)
- Has participant ever tried or experimented with smokeless tobacco (Yes or No)
- Intention to try smokeless tobacco soon (Yes or No)
- Would participant use smokeless tobacco if offered it (Definitely yes, Probably yes, Probably not, Definitely not)
- Does participant think they will be using smokeless tobacco one year in future (Definitely yes, Probably yes, Probably not, Definitely not)
- Respiratory symptoms in previous week (Wheeze on waking, Cough during day, Shortness of breath during day, Night cough, wheeze or shortness of breath during night, Runny nose or sneezing, Blocked or stuffy nose, Sore throat or hoarse voice, Headaches/face aches, Aches/pains elsewhere, Chill/shivers)
- Using medication (Yes or No)
- Reason for medication use (Asthma, Other respiratory illness, Other health condition)
- EQ-5D-Y
- Mediator questions
- Intervention engagement and acceptability (intervention group only)
- Academic performance questionnaire (teacher completed)
- Number of days absent since previous follow-up
- Salivary cotinine concentration measurement (ng/mL)

6.3.4. Six month follow up (participant level)

- Outside space at home (Yes or No)
- Number of bedrooms in home
- Number of adults (≥18 years) living with participant
- Number of adults (≥18 years) that smoke
- Number of children (<18 years) living with participant
- Number of children (<18 years) that smoke
- Where do residents smoke (Anywhere in home, In some rooms in home, Only in one room, Only outside)
- Do residents smoke in front of children (Yes or No)
- Do people who visit the home smoke (Yes or No)
- Where do visitors smoke (Anywhere in home, In some rooms in home, Only in one room, Only outside)
- Do visitors smoke in front of children (Yes or No)
- Second hand smoke exposure in vehicles (Yes or No)
- Second hand smoke exposure elsewhere (Mosque, Market/Mall/Bazar, School/University, Playground, Bus stand/Three wheeler CNG stand/Rickshaw stand, Tea stall, Other)
- Number of shops selling cigarettes or tobacco within five minutes walking distance of home
- Number of shops selling cigarettes or tobacco within five minutes walking distance of school
- Do residents use e-cigarettes (Yes or No)
- Has participant ever tried or experimented with tobacco (Yes or No)
- Does participant smoke regularly or frequently (Yes or No)
- Number of smoking days in last 30 days
- Number of cigarettes smoked in lifetime
- Number of bidis smoked in lifetime
- Number of shisha/hookah session in lifetime
- Intention to try tobacco smoking soon (Yes or No)
- Would participant smoke tobacco if offered it (Definitely yes, Probably yes, Probably not, Definitely not)

- Does participant think they will be smoking one year in future (Definitely yes, Probably yes, Probably not, Definitely not)
- Has participant ever tried or experimented with smokeless tobacco (Yes or No)
- Intention to try smokeless tobacco soon (Yes or No)
- Would participant use smokeless tobacco if offered it (Definitely yes, Probably yes, Probably not, Definitely not)
- Does participant think they will be using smokeless tobacco one year in future (Definitely yes, Probably yes, Probably not, Definitely not)
- Respiratory symptoms in previous week (Wheeze on waking, Cough during day, Shortness of breath during day, Night cough, wheeze or shortness of breath during night, Runny nose or sneezing, Blocked or stuffy nose, Sore throat or hoarse voice, Headaches/face aches, Aches/pains elsewhere, Chill/shivers)
- Using medication (Yes or No)
- Reason for medication use (Asthma, Other respiratory illness, Other health condition)
- EQ-5D-Y
- Mediator questions
- Academic performance questionnaire (teacher completed)
- Number of days absent since previous follow-up

6.3.5. Twelve month follow up (participant level)

- Outside space at home (Yes or No)
- Number of bedrooms in home
- Number of adults (≥18 years) living with participant
- Number of adults (≥18 years) that smoke
- Number of children (<18 years) living with participant
- Number of children (<18 years) that smoke
- Where do residents smoke (Anywhere in home, In some rooms in home, Only in one room, Only outside)
- Do residents smoke in front of children (Yes or No)
- Do people who visit the home smoke (Yes or No)
- Where do visitors smoke (Anywhere in home, In some rooms in home, Only in one room, Only outside)
- Do visitors smoke in front of children (Yes or No)
- Second hand smoke exposure in vehicles (Yes or No)
- Second hand smoke exposure elsewhere (Mosque, Market/Mall/Bazar, School/University, Playground, Bus stand/Three wheeler CNG stand/Rickshaw stand, Tea stall, Other)
- Number of shops selling cigarettes or tobacco within five minutes walking distance of home
- Number of shops selling cigarettes or tobacco within five minutes walking distance of school
- Do residents use e-cigarettes (Yes or No)
- Has participant ever tried or experimented with tobacco (Yes or No)
- Does participant smoke regularly or frequently (Yes or No)
- Number of smoking days in last 30 days
- Number of cigarettes smoked in lifetime
- Number of bidis smoked in lifetime
- Number of shisha/hookah session in lifetime
- Intention to try tobacco smoking soon (Yes or No)
- Would participant smoke tobacco if offered it (Definitely yes, Probably yes, Probably not, Definitely not)
- Does participant think they will be smoking one year in future (Definitely yes, Probably yes, Probably not, Definitely not)
- Has participant ever tried or experimented with smokeless tobacco (Yes or No)
- Intention to try smokeless tobacco soon (Yes or No)
- Would participant use smokeless tobacco if offered it (Definitely yes, Probably yes, Probably not, Definitely not)
- Does participant think they will be using smokeless tobacco one year in future (Definitely yes, Probably yes, Probably not, Definitely not)
- Respiratory symptoms in previous week (Wheeze on waking, Cough during day, Shortness of breath during day, Night cough, wheeze or shortness of breath during night, Runny nose or

sneezing, Blocked or stuffy nose, Sore throat or hoarse voice, Headaches/face aches, Aches/pains elsewhere, Chill/shivers)
- Using medication (Yes or No)
- Reason for medication use (Asthma, Other respiratory illness, Other health condition)
- EQ-5D-Y
- Mediator questions
- Academic performance questionnaire (teacher completed)
- Number of days absent since previous follow-up

7. Data

7.1. Data collection

Data will be collected from participating school clusters and/or teachers and children within these participating clusters at five time points; during screening (school level data only), at baseline (just prior to randomisation) and at 3, 6 and 12 months post-randomisation. Data collection will be supervised/facilitated by field investigators working with the research teams in Bangladesh and Pakistan. The majority of the trial data will be collected and managed using REDCap electronic data capture tools hosted at Ark Foundation, Bangladesh [Harris, 2009] [Harris, 2019]. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. The respiratory symptoms will be recorded using Optical Mark Recognition (OMR) compatible paper based symptoms diaries. The responses recorded in these diaries can be scanned using OMR software, with responses being automatically converted into an electronic format that can be shared with the trial statistician. Salivary cotinine samples will be transferred to a UK based laboratory for analysis, with the results then being shared with the relevant teams in Bangladesh and Pakistan and added to the relevant REDCap database.

7.2. Management of datasets and data verification

Data validation will be implemented as part of the REDCap system, so that data will be validated/checked at the point of data entry. The validation rules implemented in the REDCap system will be reviewed and agreed by the trial statistician prior to data collection commencing. Six databases will be used to capture and store the trial data - two databases for each of the three research teams (Bangladesh, Pakistan-Urdu and Pakistan-Sindhi), with data being entered directly onto the study databases. One of these databases will contain cluster level data (one row per cluster) and the other will contain participant level data (one row per participating child). The trial statistician will have permissions to download exports from each of the six databases as required, with these data then being merged/managed using Stata Version 17.0 or later [StataCorp, 2021]. Cluster allocations will be stored in the databases containing the cluster level data, but will not be accessible by the trial statistician until the primary analyses are complete (i.e. the trial statistician will not have permissions to view or export the group allocation variable in each of the cluster level databases). Electronic datasets obtained from

the symptoms diaries using the OMR software will be shared directly with the trial statistician via the University of York Drop-Off service.

The trial statistician will import all data exports (from REDCap or the OMR software) into Stata (precise version reported in any outputs/reports) and will conduct further checks to investigate the consistency and completeness of the exported data, and will check the range and format of any variables/quantities derived using the exported data. Any anomalies identified during these processes will be documented and resolved in accordance with the procedures outlined in YTU SOP S02: Statistical Quality Control. Any changes to the analysis data will be detailed in an assumptions log as described in YTU SOP S02: Statistical Quality Control.

8. Analysis

Clusters and participants will be analysed as part of the groups to which they were randomised regardless of subsequent adherence to the allocated condition. The flow of clusters and participants through the study will be presented according to CONSORT guidance (see Appendix A). Continuous characteristics that vary at the cluster level (e.g. cluster size, B:G ratio etc.) will be summarised in terms of the available sample size (number of clusters with non-missing data), arithmetic mean, standard deviation, median, interquartile range, minimum and maximum. Categorical characteristics that vary at the cluster level will be summarised at the cluster level in terms of frequencies and proportions. Continuous data and count data with a large potential range of values (e.g. cigarettes smoked over lifespan), that vary at the individual level will be summarised in terms of the available sample size (number of individuals with non-missing data), arithmetic mean, standard deviation, median, interquartile range, minimum and maximum. Categorical data and count data with a small potential range of values (e.g. number of children in household who smoke), that vary at the individual level will be summarised at the individual level in terms of frequencies and proportions.

8.1. Screening Data

The key characteristics of the clusters screened for potential participation will be reported including

- Country (Bangladesh, Pakistan)
- School type (Public, Private)
- Cluster size (approximate number of children in Y5 at cluster)
- Sex (Girls, Boys, Mixed)

The following information will be reported in tabular format (by country and overall) and in the CONSORT flow diagram (countries aggregated)

- The number/proportion of eligible/ineligible clusters
- Reasons for ineligibility
- The number of eligible clusters approached for consent
- The number/proportion of clusters approached for consent that did/did not consent
- Reasons for non-consent

For the consenting clusters, the number of children per cluster and number of consented/participating children per cluster will be reported (mean, SD, median, interquartile range, maximum and minimum). The number of children excluded from participation due to safeguarding issues will also be reported.

8.2. Baseline Data

Baseline data that varies at the cluster level will be summarised by randomised group. Baseline data that varies at the individual level will be summarised by randomised group at the individual level. Two tables of these baseline data will be generated; one including all randomised eligible children, and one only including baseline data from participants included in the primary analysis model (see Section 8.3.2 for details). Plots illustrating the distribution of the individual level baseline cotinine measurements will be produced.

8.3. Primary Outcome Analyses

The primary outcome for CLASS-III is salivary cotinine concentration (ng/mL) at 3 months post-randomisation. Saliva samples will be sought at three months post-randomisation for all consented children that are not withdrawn by the time of their three month follow up visit, including children whose baseline cotinine concentration was less than 0.1 ng/mL or greater than 12 ng/mL (or was missing).

8.3.1. Preliminary analyses

The number of participants with salivary cotinine measurements a below/above the assay detection limits (0.1 ng/mL and 50 ng/mL respectively), insufficient sample volumes and missing samples will be reported for both the baseline and month 3 time points. Salivary cotinine concentrations at baseline and three months post-randomisation will be reported descriptively by randomised group. These data will be summarised at the individual level and at the cluster level (in terms of the cluster level means and medians). Summary statistics for the month 3 cotinine measurements (in terms of both availability/quantifiability and concentration) will also be reported cross-classified by randomised group and self-reported tobacco use (smoked and/or smokeless) in the past 7 days.

8.3.2. Primary analysis

Participants with baseline cotinine concentrations less than 0.1 ng/mL (i.e. those below assay detection limits) or greater than 12 ng/mL (i.e. those that appear to be actively using tobacco at baseline) will be excluded from the primary analysis, as will participants who are missing salivary cotinine readings at 3 months (due to absence, withdrawal of consent, loss to follow-up etc.). The salivary cotinine measurement at three months post-randomisation for participant i in cluster j will be modelled using a linear mixed model, with fixed effects for treatment group, baseline cotinine concentration, country (stratification factor), school type (stratification factor) and participant sex (stratification factor[2]), and a random intercept for school cluster (see Table 5 for details). This model will be fitted using restricted maximum likelihood estimation. For the purposes of this analysis, participants with outcome measurements below the limit of quantification will be assigned a value of 0.05 ng/mL and participants with outcome measurements above the limit of quantification will be assigned a value of 50 ng/mL

[2] The cluster level sex ratio (M:F) was used in the minimisation algorithm used to allocate school clusters

The appropriateness of key model assumptions will be checked using diagnostic plots based on the standardised residuals of the fitted model (standardised residuals vs fitted values and Q-Q plot of the standardised residuals). If these plots suggest the data show important departures from the assumptions of this planned analysis, then a generalised linear mixed model with an appropriate link and error distribution will be used instead (e.g. log-gamma GLM), with the same fixed and random effects as specified in Table 5. The estimated treatment effect from this model will be transformed back to the original scale of measurement for reporting.

The point estimate and two-sided 95% confidence interval (based on a t distribution with degrees of freedom calculated using the Kenward-Roger method if feasible [Kenward, 1997]) for the treatment effect from the fitted primary analysis model will be reported, together with the p-value for a two-tailed Wald test of the hypothesis H_0: $\mathbb{E}(Y|\,\text{Intervention}, X) - \mathbb{E}(Y|\,\text{Control}, X) = 0$ (and/or H_0: $\mathbb{E}(Y|\,\text{Intervention}, X)/\mathbb{E}(Y|\,\text{Control}, X) = 1$ if appropriate/necessary). In addition, we will also report the p-value and compatibility (confidence) interval curve for the treatment effect from the fitted primary analysis model [Rafi, 2020].

Table 5: Terms included in the linear predictor of the primary analysis model

Term	Interpretation	Details
group_j	Randomised group allocation of cluster j	Control vs Intervention (Control used as reference category) No missing values
country_j	Country where cluster j is situated	Bangladesh vs Pakistan (Bangladesh used as reference category) No missing values
school_type_j	Cluster j school type	Public vs Private (Public used as reference category) No missing values
sex_{ij}	Sex of child i in cluster j	Boy vs Girl (Boy used as reference category) Missing values imputed using cluster mode
$f(\text{log\_baseline}_{ij})$	Natural logarithm of baseline cotinine concentration (ng/mL) of child i in cluster j	Restricted cubic spline with four knots placed at the 5th, 35th, 65th and 95th percentiles of the (logged) observed values (excluding observations not in [0.1, 12]ng/mL) [Harrell 2016] [Kahan, 2016] Missing values imputed with cluster specific mean (prior to spline expansion). If all values are missing for a given cluster then the country specific mean of the observed baseline values will be used instead
u_j	Random intercept for cluster j	$u_j \sim N(0, {\sigma_u}^2)$ with σ_u estimated using the observed data

8.3.3. Sensitivity Analyses

A number of additional analyses of the primary outcome will be undertaken to investigate the sensitivity of the results of the primary analysis to departures from the key statistical assumptions that underpin

this analysis. In particular we will investigate the distributional assumptions (for the outcome), and different assumptions about any missing primary outcome data.

8.3.3.1 Error distribution

The planned primary analysis model assumes the response to be conditionally normal given the fixed and random effects in the linear predictor. To investigate the potential sensitivity of results to this choice of error distribution, we will fit a mixed effect generalised linear model, with log link and gamma error distribution and the same fixed and random effects specification as the primary analysis model. The point and interval estimates of the exponentiated coefficients and associated p-values will be reported as for the primary analysis model (i.e. point estimate, 95% confidence interval, p-value for two sided test of H_0: $e^{\beta} = 1$ and compatibility/p-value function). The fitted model will also be used to obtain point and interval estimates of the difference in expected cotinine concentration at three months post randomisation conditional on representative values of the covariates (median for baseline cotinine concentration and at each combination of country, school type and sex) and marginally with respect to the school level random intercept.

8.3.3.2 Cumulative probability model

Measurements of salivary cotinine at three months post randomisation may feature observations at or below the lower limit of quantification of the cotinine assay (i.e. <0.1 ng/mL), resulting in mixed discrete and continuous observations. There may also be some observations above the upper limit of quantification (i.e. > 50ng/mL). Fully parametric models (such as the Gaussian GLM fitted for the primary analysis or the Gamma GLM described in Section 8.3.3.1) will not properly account for these features. To investigate the possible influence of this on the results of the primary analysis, a semi-parametric cumulative probability model will be fitted [Liu, 2017], allowing for mixed continuous/discrete observations and relaxing assumptions about the conditional distribution of the outcome. This will be accomplished using an ordinal regression model with an appropriate link (i.e. logit, probit, complementary log-log), and the same fixed and random effects specification as for the primary analysis. The link function will be chosen based on plots of the link transformed cumulative probabilities, with the link function resulting in greatest parallelism being used for analysis. The fitted model will be used to plot the empirical cumulative distribution functions (of the outcome measurements) for each group conditional on representative values of the covariates (median for baseline cotinine concentration and at each combination of country, school type and sex) and marginally with respect to the school level random intercept. We will also use the fitted model to derive estimated differences in expected cotinine concentration, setting any observations below the limit of quantification to be 0.05, and any above to be 50. The point estimates will be reported together with 95% confidence intervals based on bias corrected non-parametric bootstraps (2500 replicates, stratified re-sampling undertaken at the cluster level) will also be reported.

8.3.3.3 Missing primary outcome data

The analyses described in this section will only use data from participants whose baseline salivary cotinine concentration was in the range [0.1, 12]ng/mL, or was missing, as per the primary analysis. The approach used for the primary analysis assumes that, conditional on treatment group, the baseline

covariates and the cluster random intercept, the distribution of salivary cotinine at three months post-randomisation is the same among participants with observed and missing outcome data. We refer to this missing data assumption as MAR-1. Firstly we will use multiple imputation (see details of imputation procedure below) to relax MAR-1, by incorporating additional pre and post-randomisation predictors of missingness and outcome into the imputation model used to impute the missing primary outcome data. We refer to this missing data assumption as MAR-2. Secondly, we will use delta-based multiple imputation implemented via a pattern mixture model approach to investigate the sensitivity of the results of the primary analysis when a range of missing not at random (MNAR) scenarios are applied to the unobserved primary outcome data [Cro, 2020].

We will first impute missing data assuming these data are MAR conditional on the variables included in the imputation model (see Table 6). At least 100 imputations will be generated using substantive model compatible fully conditional specification, with imputation carried out separately by randomised group if feasible. The number of cycles per imputation will be determined based on trace plots of summary statistics of the imputed values, with a minimum of 10 cycles being used if this appears to be sufficient to reach stability. Missing outcome and covariate data will be imputed. The multiply imputed datasets (generated under assumption MAR-2) will be analysed using the same substantive analysis model as used for the primary analysis, with the estimates for each imputed dataset being combined using Rubin's rules [Rubin, 1987]. If the Monte Carlo error for any of the treatment effect estimates is greater than or equal to 5% of the standard error estimate, then a further 50 imputations will be generated. This process will be repeated until the Monte Carlo error is below this threshold. The final point estimate of the treatment effect under MAR-2 will be reported, together with a two-sided 95% confidence interval and p-value.

Table 6: Details of imputation model

Variable	**Type**	**Details of variable**	**Details of univariate model used to impute any missing values**
Cluster ID	Nominal	Cluster indicators (approximately 68 levels)	N/A
Country	Binary	Bangladesh = 0 Pakistan = 1	N/A
School type	Binary	Public = 0 Private = 1	N/A
Natural logarithm of baseline cotinine concentration (spline expanded)	Continuous*	Restricted cubic spline expansion of the natural logarithm of measured baseline cotinine concentration (ng/mL) (four knots placed at the 5^{th}, 35^{th}, 65^{th} and 95^{th} percentiles of the (logged) observed values, restricted to [0.05, 12] by design).	Predictive mean matching (20 nearest neighbours)
Sex	Binary	Male = 0 Female = 1 (likely to be complete or nearly complete)	Logistic regression (with penalisation if required)
Age	Continuous	Participant age (or approximate age) at baseline (likely to be complete or nearly complete)	Predictive mean matching (20 nearest neighbours)

Outside space at home	Binary	Yes = 0 No = 1 (likely complete/nearly complete)	Logistic regression (with penalisation if required)
EQ-5D general health at baseline	Continuous*	Participant reported general health at baseline. Overall health scored 0-100 using VAS (likely to be complete or nearly complete)	Predictive mean matching (20 nearest neighbours)
Smoking uptake scale at baseline	Ordinal	Susceptibility to/stage of smoking uptake at baseline, see Table 3 (likely to be complete or nearly complete)	Imputed using ordinal logistic regression (with penalisation if required). Included as a single linear term in univariate models used to impute other variables if necessary for convergence
Month 3 cotinine concentration	Continuous*	Cotinine concentration (ng/mL) at 3 months post randomisation	Predictive mean matching (20 nearest neighbours)

*Potential for floor/ceiling in observations, leading to possibly mixed continuous and discrete observations

For the delta-based multiple imputation we will distinguish between four broad reasons for missing primary outcome data;

1. Missing due to participant withdrawal
2. Missing due to participant absence/test not completed on day of month three follow up
3. Missing due to invalid sample/problem with laboratory test
4. Missing due to cluster withdrawal/non-response

We assume outcome data that are missing due to reasons 3 and 4 are MCAR or MAR, and impute data that are missing due to reasons 1 and 2 under various departures from MAR. Imputations under these assumptions will be generated by incorporating two numerical parameters $\boldsymbol{\delta} = (\delta_0, \delta_1)$ that specify the difference in expected three month cotinine concentration between participants with observed and missing outcome data (conditional on the variables in the imputation model), where these outcomes are missing for reasons 1 and 2 outlined above. Here δ_0 specifies the difference for participants in the control group and δ_1 specifies the difference for participants in the intervention group. Three broad patterns of missing data will be considered; 1) δ_0 fixed at 0 while δ_1 varies between 0 and 10 ng/mL in increments of 2.5 ng/mL, 2) δ_1 fixed at 0 while δ_0 varies between 0 and 10 ng/mL in increments of 2.5 ng/mL and 3) δ_0 and δ_1 vary simultaneously between 0 and 10 ng/mL in increments of 2.5 ng/mL. For the MNAR assumptions, the imputed datasets will be analysed using the same substantive model as used for the primary analysis, with the results being combined using Rubin's rules. The final point estimates of the treatment effects under the various different departures from MAR-2 will be reported, together with two-sided 95% confidence intervals and p-values.

8.3.4. Subgroup analyses

The analyses described in this section will only use data from participants whose baseline salivary cotinine concentration was in the range [0.1, 12]ng/mL (or was missing) as per the primary analysis.

Subgroup analyses will be conducted to investigate the extent to which the treatment effect varies by country and by types of second hand smoke exposure (as reported at baseline). Participants will be

assigned to the following four subgroups according to the type of second hand smoke exposure reported at baseline

1. Second hand smoke exposure reported both inside (residents or visitors) and outside the home
2. Second hand smoke exposure reported inside the home, but not outside
3. Second hand smoke exposure reported outside of the home, but not inside
4. No second hand exposure reported inside or outside of the home

To investigate treatment effect heterogeneity across countries, an additional treatment group (intervention vs control) by country (Bangladesh vs Pakistan) interaction term will be added to the linear predictor of the primary analysis model. To investigate treatment effect heterogeneity across types of second hand smoke exposure reported at baseline, the main effects of type of exposure and the interactions between these and treatment group will be added to the linear predictor of the primary analysis model.

In each case, the augmented model (with interactions) will be fitted using restricted maximum likelihood, and used to derive differences in mean cotinine concentration at three months post randomisation for each subgroup (country or type of second hand smoke exposure), together with two-sided 95% confidence intervals and p-values.

8.3.5. Mediation analysis

We will undertake an exploratory analysis using self-reported active use of tobacco (smoked and/or smokeless) during the seven days prior to the month 3 follow-up to decompose the effect of allocation into direct and indirect (via active tobacco use) effects. We assume that confounding of any mediator-outcome pathway is negligible conditional on the predictors included in the analysis (treatment allocation, baseline salivary cotinine, country, school status and sex), and allow for treatment by mediator interaction (i.e. allow the effects of the mediator on outcome to vary by treatment group). This model will be fitted using the user written Stata command `paramed` [Emsley, 2013]. The point estimates of the natural direct and indirect effects will be reported, together with 95% confidence intervals obtained using a non-parametric bootstrap (2500 replicates, resampling undertaken at the cluster level)

8.4. Secondary analyses

8.4.1. Salivary cotinine at 3 months (all participants)

The primary analysis will exclude participants that had baseline salivary cotinine concentration outside of the range [0.1, 12]ng/mL (as well as participants that were missing salivary cotinine measurements at three months post-randomisation). We will conduct a secondary analysis of the month three salivary cotinine measurements (the primary outcome) following similar procedures to those of the primary analysis (e.g. same model, same baseline covariates), but including all participants with available month three cotinine measurements (including those with baseline cotinine measurements outside of the

range [0.1, 12]ng/mL. Any baseline measurements less than 0.1ng/mL (the lower limit of quantification for the cotinine assay) will be assigned a value of 0.05. Any baseline measurements above the upper limit of quantification (50 ng/mL) will be assigned a value of 50. The point and interval estimates and p-value for the treatment effect will be reported analogously to the reporting of the primary analysis.

8.4.2. Salivary cotinine at 3 months (excluding self-reported tobacco users)

The primary analysis will exclude participants that had baseline salivary cotinine concentration outside of the range [0.1, 12]ng/mL (as well as participants that were missing salivary cotinine measurements at three months post-randomisation). We will conduct a secondary analysis of the month three salivary cotinine measurements (the primary outcome) following similar procedures to those of the primary analysis (e.g. same model, same baseline covariates), but excluding all participants with any baseline data indicating primary tobacco use (smoked or smokeless). Hence participants with baseline cotinine measurements outside of the range [0.1, 12]ng/mL will be excluded (as per the primary analysis), but also participants that self-report any primary tobacco use at baseline (i.e. report ever having tried or experimented with smoked or smokeless tobacco) regardless of their measured baseline cotinine concentration. The point and interval estimates and p-value for the treatment effect obtained for this analysis will be reported analogously to the reporting of the primary analysis.

8.4.3. Respiratory and aural symptoms

We will present various descriptive analyses of the available daily upper, lower and aural symptoms scores observed at each time point (both pre and post the imputation described in Section 6.2.1). This will include tabular and graphical summaries of the mean and median symptom scores (by day and randomised group at each time point) and the proportion of participants with reported symptom summary scores at or above clinical threshold (by day and randomised group at each time point). For the purposes of these analyses, clinical threshold is defined as a daily upper respiratory tract score ≥4, a daily lower respiratory tract score ≥4 and a daily aural symptoms score ≥2.

For each symptom type (upper respiratory, lower respiratory and aural) we will calculate the number of clinical episodes at each time point (i.e. the number of days where the relevant symptom summary score is above the clinical threshold outlined above). We will estimate differences between randomised groups in incidence of clinical episodes (at each time point) using a mixed effect negative binomial regression model. This model will include fixed effects for treatment group, time points, treatment by time point interactions, country, school type and sex (the stratification/minimisation factors), random intercepts for cluster and participant (to model the correlation between measurements within cluster and participant respectively), and an offset term for the natural logarithm of the number of days with an available score (for the relevant symptom at the relevant time point).

Treatment effect estimates (at each time point) will be reported in terms of incidence rate ratios. Bias-corrected two-sided 95% confidence intervals and p-values will be obtained via a non-parametric bootstrap of the whole analysis, (both imputation of missing items and model fitting), with resampling

undertaken at the cluster level stratified by treatment group (2500 replicates). If the three level model fails to converge (when applied to the observed data, or more than 1% of the bootstrap replicates), then this outcome will be analysed separately by time point (with the participant level random intercepts removed). Further analyses using multiply imputed symptoms diary data will be undertaken if at any time point (3, 6 or 12 months), more than 25% of cases are missing at least one symptom summary score on more than 50% of days. Imputation of daily summary scores will follow a similar approach as described in Section 8.3.3.3, but will include the additional daily summary score variables with steps taken to improve stability and convergence where necessary (e.g. data augmentation, treating ordinal variables as continuous predictors etc.).

8.4.4. Second hand smoke exposure

Descriptive summaries of the prevalence of smoking within the home (e.g. the number of adults/children in the household that smoke) will be provided by time point and allocation, as will the presence/extent of smoking restrictions and visibility of smoking within the home (see Section 6.2.2). Second hand smoke exposure outside the home (e.g. in vehicles or at other specific locations) will also be reported descriptively by time point and allocation.

The presence/extent of smoking restrictions and visibility of smoking within the home reported at 3 months post randomisation will be compared between groups using a partial proportional odds model, with fixed effects for allocation (Intervention or Control), country (Bangladesh or Pakistan), school status (Public or Private) and sex (male or female), and cluster robust standard errors. This model will be fitted using the community contributed Stata command `gologit2` [Williams, 2005]. Proportional odds will be assumed for all of the fixed effects except the treatment effect, which will be allowed to vary across different levels of the outcome. The estimated odds ratios for allocation will be reported together with 95% confidence intervals and p-values. This model will be used to derive average marginal effects of allocation (on the absolute risk scale) across each level of the outcome for each combination of the three binary covariates, together with both delta method and non-parametric bootstrap 95% confidence intervals and p-values.

8.4.5. Smoking related behaviour

Descriptions of the summary variables derived using participants' reported primary tobacco exposure (both smoked and smokeless) are given in Section 6.2.3.

The number and proportion of participants in each of the three categories; Frequent or regular smoker (1), Tried, but not a frequent or regular smoker (2), Not tried smoking (3) will be summarised by allocation at each time point. The number of days that participants in categories (2) and (3) have smoked in the past 30 days will be summarised descriptively by allocation at each time point, as will the number of reported lifetime cigarettes, bidis and hookah/shisha sessions. The number and proportion of participants in category (3) that think they will try smoking soon will be summarised by randomised

group at each time point. The responses of participants in categories (2) and (3) to the questions about whether they would smoke tobacco if offered it by a friend, or whether they think they will be smoking a year from now will also be summarised by allocation at each time point.

The number and proportion of participants across each level of the smoking uptake scale will be reported by randomised group at each time point. The smoking uptake scale scores at three months will be analysed using a partial proportional odds model, with fixed effects for allocation (Intervention or Control), country (Bangladesh or Pakistan), school status (Public or Private) and sex (male or female), and cluster robust standard errors. This model will be fitted using the community contributed Stata command `gologit2` [Williams, 2005]. Proportional odds will be assumed for all of the fixed effects except the treatment effect, which will be allowed to vary across different levels of the outcome. The estimated odds ratios for allocation will be reported together with 95% confidence intervals and p-values. This model will be used to derive average marginal effects of allocation (on the absolute risk scale) across each level of the outcome for each combination of the three binary covariates, together with both delta method and non-parametric bootstrap 95% confidence intervals and p-values.

8.4.6. Quality of life

Responses to the EQ-5D-5L will be summarised descriptively by item at each time point. No formal between group comparisons of EQ-5D-5L data will be undertaken.

8.4.7. Absenteeism and academic performance

Teacher reported school absenteeism data will be summarised descriptively (at both the cluster and individual level) by randomised group at each time point. The total number of days of absence and the proportion of days absent between baseline and 3, 6 and 12 months post randomisation will also be reported (at the individual level) by randomised group. The proportion of days absent between the baseline and 3, 6 and 12 month follow-up visits will be analysed using a semi-parametric cumulative probability models [Liu, 2017] based on ordinal regression. These models will use cases with complete absenteeism data between baseline and the relevant time point, and will condition on fixed effects for treatment group, country (Bangladesh or Pakistan), school status (public or private), sex (boy or girl) and the number of days absent during the one month prior to the baseline visit, and random intercepts for cluster. Any participants that have the number of days of absence during the month prior to baseline missing, will have these missing values imputed with the relevant cluster specific median prior to model fitting. A range of link functions will be assessed (logit, probit complementary log log), with the final model being based on the link function resulting in the highest log likelihood. The fitted model will be used to estimate the between group difference in expected number of days absent, together with delta method and bootstrap 95% confidence intervals and p-values.

Responses to the APQ at each time point will be summarised descriptively by allocation and overall. No formal comparison of these data by randomised group (e.g. estimation of odds ratios for allocation) will be undertaken.

8.4.8. Process evaluation

8.4.8.1 Mediators

Risk awareness

The number and proportion of participants responding True, Don't know and False to each of the six risk awareness questions, and the total number of correct responses (0 – 6) will be reported by time point and allocation.

Differences between groups in the total number of correct responses (0 – 6) at the three month time point will be analysed using mixed effect ordinal regression with an appropriately chosen link function (logit, probit or complementary log-log). This model will include fixed effects for treatment group, country (Bangladesh or Pakistan), school status (public or private) and sex (boy or girl), and random intercepts for school cluster. The fitted model will be used to estimate absolute and relative differences between groups in the probability of providing the correct response to all six of the knowledge/awareness mediator questions, together with delta method 95% confidence intervals and p-values. If the ordinal model encounters convergence issues (e.g. due to sparse or empty cells), then the number of correct responses (at three months post-randomisation) will be dichotomised into a 0-5 correct responses vs 6 correct responses. This binary outcome would then be analysed using a logistic regression model with the same fixed and random effects specified above, with this fitted model then being used to estimate absolute and relative differences between groups in the probability of providing the correct response to all six questions, together with delta method 95% confidence intervals and p-values.

Outcome expectancies, self-efficacy, intentions and action planning

Participants' responses to each of the eight questions assessing outcome expectancies, self-efficacy, intentions and action planning for second hand smoking will be reported by time point and allocation.

The responses to each of the questions will be scored 0 – 4, and summed to generate a score between 0 and 32 (higher scores indicating more positive expectations of avoiding second hand smoke and stronger intentions to avoid second hand smoke). Differences between groups in this scores at the three month time point will be analysed using mixed effect ordinal regression with an appropriately chosen link function (logit, probit or complementary log-log). This model will include fixed effects for treatment group, country (Bangladesh or Pakistan), school status (public or private) and sex (boy or girl), and random intercepts for school cluster. The fitted model will be used to estimate the difference in expected score a three months, together with delta method 95% confidence intervals and p-values. If the ordinal model encounters convergence issues (e.g. due to sparse or empty cells), then a Gaussian

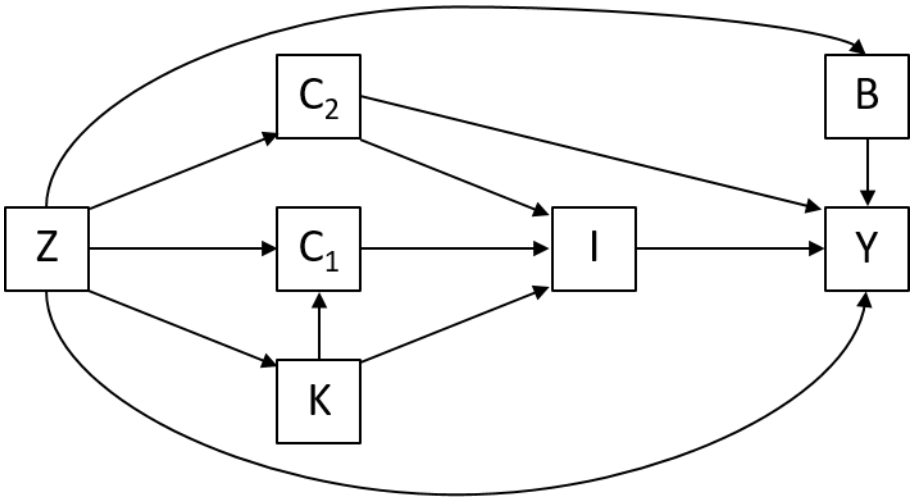
generalised linear model with an appropriately chosen link will be used instead. Treatment effect estimates from this model will be reported on the scale of the original data.

Exploratory mediation analysis

The directed acyclic graph [Greenland 1999] in Figure 1 is based on the logic model for the Smoke Free Intervention being tested in CLASS-III.

Measures of beliefs about consequences/capabilities (C_1, C_2), intentions (I) and behavioural regulation (B) are collected at the same time as the month 3 cotinine measurements, and therefore cannot be used to estimate the extent to which any effect of allocation on this outcome is mediated via these pathways. Knowledge about the risks of SHS exposure (K) is also measured at this time point, but is assumed to provide a reasonable proxy for the state of knowledge during the weeks prior to outcome data collection. We therefore undertake an exploratory analysis to decompose the total causal effect of allocation on the primary outcome (salivary cotinine at 3 months) into indirect (i.e. effects of allocation that can be attributed to changes in knowledge about the harms of second hand smoke exposure) and direct effects (i.e. effects of allocation that are not explained by changes to this mediator). We assume that confounding of any mediator-outcome pathway is negligible conditional on the predictors included in the analysis (treatment allocation, baseline salivary cotinine, baseline score for the mediator, country, school status and sex), and allow for treatment by mediator interaction (i.e. allow the effects of the mediator on outcome to vary by treatment group). This model will be fitted using the user written Stata command `paramed` [Emsley, 2013]. The point estimates of the natural direct and indirect effects will be reported, together with 95% confidence intervals obtained using a non-parametric bootstrap (2500 replicates, resampling undertaken at the cluster level)

Figure 1: Directed Acyclic Graph depicting hypothesised causal pathways by which allocation to Smoke Free Intervention (Z) affects cotinine concentration at 3 months post randomisation (Y). The intermediate variables are; Knowledge of the risk of SHS exposure (K), Beliefs about consequences of SHS exposure (C_1), Beliefs about capabilities of avoiding SHS exposure (C_2), Intentions to avoid SHS exposure (I), Behavioural regulation (B). For clarity, measured baseline variables that influence either the outcome or the mediators are omitted



8.4.8.2 Intervention acceptability

Summaries of the frequency and proportion of participants in the intervention group that report (at month 3) taking part in smoke-free intervention activities will be reported by country and school cluster and overall. Responses to the eight Likert scale items assessing enjoyment of the various intervention components will be summarised (at the individual level) by country and overall.

8.4.8.3 Fidelity of intervention delivery

The extent to which each of the session components were implemented will be reported in terms of cluster level frequencies and proportions by country and overall, with separate tables presented for each session.

8.5. Adverse events

Data pertaining to adverse events (AEs) and serious adverse events (SAEs) will be sought at all follow-up time points. Given the nature of the intervention and the participant population we do not expect there to be many adverse or serious adverse events, and still fewer with any causal relationship to the intervention. The number of AEs and SAEs and the proportion of these that were deemed possibly, probably or definitely related to the intervention will be reported by randomised group. Detailed information relating to each reported AE/SAE will also be provided.

9. SAP Revisions

Amendment/addition to SAP and reason for change	New version number, name and date

10. Roles and responsibilities

Name	Trial Role	Signature	Date
Prof. Kamran Siddiqi	Chief Investigator	Kamran Siddiqi	19-4-23
Prof Mona Kanaan	Senior Statistician	Mona Kanaan	20 April 2023
Mr Charlie Welch	Trial Statistician	C. Welch	20th April 2023

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