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Children Learning About Second-hand Smoke (CLASS III)

A cluster randomised controlled trial

PROTOCOL

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2. TRIAL SUMMARY

Second-hand smoke (SHS) exposure costs 800,000 lives a year. 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. 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 and a pilot trial, 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.

We aim to assess the effectiveness and cost-effectiveness of a school-based Smoke-Free Intervention (SFI) in reducing children's exposure to SHS and the frequency and severity of respiratory symptoms. SFI, a behavioural intervention, 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 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. A change in salivary cotinine -a highly sensitive and specific biomarker of SHS exposure- is the primary outcome which will be measured at month 3. Secondary outcomes include frequency and severity of respiratory symptoms, healthcare contacts, school absenteeism, smoking uptake and quality of life. An economic and process evaluation will also be conducted. The investigators' expertise and track record within the field is complemented by their extensive links with schools and with policy makers in the two countries.

3. BACKGROUND

SHS exposure is a serious health hazard to non-smokers, leading to an estimated 890,000 deaths and a loss of 10·9 million disability-adjusted life years (DALYs) globally every year.[1] Women and children are the worst affected: 28% of deaths from SHS exposure occur in children.[2] SHS exposure impairs children's lung development and causes immune dysregulation; therefore, increasing their risk of acquiring lower respiratory tract infections,[3] tuberculosis, and incident cases, recurrent episodes, and exacerbations of asthma.[4] Parental smoking is also associated with an increased risk of their children's admissions to hospital.[3] Moreover, SHS exposure in children and adolescents leads to poor cognitive functions and academic achievements.[5] Children living in smoking households are at high risk of becoming adult smokers later.[6]

Unfortunately, 40% of children are exposed to SHS worldwide amounting to a major public health threat.[2] The south and south-east Asia region has the highest burden of disease attributable to SHS in the world. According to the Global Tobacco Surveillance System data and Demographic Health Surveys, the majority of women and children living in Bangladesh and Pakistan are exposed to SHS.[7] In a recent survey in 12 schools in Dhaka, Bangladesh, we found that 95% of 9-11 year old children had salivary cotinine levels consistent with recent exposure to SHS.[8] In addition to public places, children are also exposed to SHS in their private homes and cars.

Smoking in indoor public spaces and workplaces is now banned in many countries, including Bangladesh and Pakistan. Where comprehensive and enforced, these bans have resulted in a significant reduction in SHS exposure and associated morbidity and mortality.[9] However, compliance to the smoke-free legislation is problematic in Bangladesh and Pakistan.[1]

Following the successful execution of the CLASS II pilot trial, our team is well positioned to conduct a definitive trial. Our stakeholders are also expecting us to conduct this trial and their engagement and interest is expressed in the enclosed letters of support. We understand that the CLASS II pilot trial was conducted in Bangladesh only; however, we justify including Pakistan at this stage for the following reasons: (a) Pakistan's disease burden due to SHS exposure is comparable to Bangladesh; (b) we have already conducted a feasibility study[10] in Pakistan in which SFI was culturally adapted and was found acceptable and feasible to deliver in schools; (c) having conducted many RCTs in Pakistan,[11] we have experience of recruiting/retaining trial participants and collecting data in a variety of settings; (d) the tobacco control cell at the Ministry and World Health Organisation (WHO) office in Pakistan have expressed a keen interest in supporting our trial (see letters of support) and (e) a multi-country trial will also carry a higher external validity than a single country trial.

There is little evidence on the effectiveness of non-legislative interventions to protect children from SHS exposure. Two recent reviews remain inconclusive. A Cochrane review included 78 trials (11 from LMIC's), many assessing the effect of parental education and counselling programmes;[12] a further systematic review and meta-analysis, included 16 trials of interventions delivered by healthcare professionals who provide routine child health care; neither found a significant reduction in children's SHS exposure.[13] Another meta-analysis, which reported on the effect of interventions for reducing SHS exposure at home, found some improvements but recommended further research.[14]

4. AIMS & RESEARCH QUESTIONS

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).

In this proposal, our objectives are to assess:

1. The effectiveness and cost-effectiveness of a school-based Smoke-Free Intervention (SFI) in:
    a. reducing children's exposure to second-hand smoke (primary outcome),
    b. reduction in frequency and severity of respiratory symptoms,
    c. number of contacts with healthcare and improvement in their quality of life,
    d. smoking uptake,
    e. school absenteeism and improvement in their school performance.

In addition, we will explore:

2. the implementation of the SFI (fidelity) and barriers/drivers to implementation
3. the mechanisms through which the SFI produces change and contextual factors that influence the implementation and effectiveness of the SFI,
4. the likely obstacles to and opportunities for implementing and scaling-up the SFI and how best to work with schools and policy makers to overcome the obstacles and maximise the opportunities.

5. DESIGN

We propose a two-arm cRCT with an embedded process and an accompanying economic evaluation. Given that the intervention is delivered by school teachers in classrooms, a cRCT is the most appropriate trial design. The intervention is of an educational class-based intervention and therefore either schoolteachers or children cannot be blinded to the allocation. The primary outcome is mean cotinine levels analysed in a UK-based lab, hence it will be possible to conceal allocation from the outcome assessors.

6. STUDY SITES

The CLASS III trial will be conducted in 68 schools (34 each in Bangladesh and Pakistan) and coordinated by the two experienced trial management teams based in ARK Foundation, Dhaka (Bangladesh) and the Aga Khan University, Karachi (Pakistan), respectively.

7. STUDY CLUSTERS (SCHOOLS)

We will recruit 68 schools from the above two sites, 34 from each area. The key eligibility criteria are as follows:

7.1 Inclusion criteria (schools)

We will include both public and private schools if they:

1. follow national curricula;
2. have year-5 classes for children (9–12 years old). The average cluster size will be 40. For certain clusters the size may vary and can go down as low as 25-30 but there is no upper limit; and
3. have and abide by smoke-free policies. School teachers involved in the training and in delivering the intervention need to be non-smokers where possible (self-reported).

7.2 Exclusion criteria (schools)

We will exclude schools if they:

1. have only primary school classes due to the challenges of following up children in other secondary schools;
2. do not use Urdu or Bangla as their education medium; or
3. have already received training on SFI in a previous project, unless the teachers who were trained have left the school.

Furthermore, it would be desirable to exclude those schools that have year-five teachers who smoke themselves. However, given the difficulty in verifying smoking status, we will not make this a mandatory exclusion criterion.

7.3 Identifying eligible clusters (schools)

We will prepare a list of schools situated within purposively selected residential wards and obtain information on their class sizes in year-5, primary or secondary school status, public or private status, boy: girl ratio and their medium (language) of teaching. We will try to recruit a random sample of schools, however, if we face problems in recruiting, a purposive sample will also be acceptable. Those found eligible, will receive brief information about the trial and an invitation to participate. Once found eligible, these will be approached for recruitment. We acknowledge that some of the eligibility criteria can only be assessed after approaching schools and talking to the headmaster and year-five teachers.

7.4 Recruiting clusters (schools)

Those schools identified and found eligible on the basis of the available information, will be sent a letter addressed to the head teacher, including brief information about the trial and inviting the school to take part in the trial. We will offer to meet head teachers face-to-face to provide verbal information and responses to their queries. We will also explain random allocation. Interested schools will be provided with a detailed information sheet and consent forms.

7.5 Ineligible and non-consenting clusters (schools)

Those who won't meet the eligibility criteria or those who meet the criteria but don't agree to participate after receiving the trial information will not be enrolled in the trial. However, their reasons for not meeting the eligibility criteria or declining to participate will be recorded.

7.6 Withdrawal of clusters (schools)

Once recruited, we will endeavour to keep all schools on board and included in the study. If for any reason, school withdraws before randomisation, we will recruit a new school to replace the withdrawing school. However, if the withdrawal takes place after randomisation, we will not replace such a school and include their data collected to date in our analyses. Data collected from the schools that withdraw at any point will be included in the analyses.

8. STUDY PARTICIPANTS (CHILDREN)

We will recruit 2720 year-five (average 40 from each school) school children (9-12 years old) after seeking their parents' consent and their assent through schools. Being the oldest year in primary school years, we consider this year to be the optimal age group to understand the message and engage with their family members to implement smoking restrictions. The key eligibility criteria are as follows:

8.1 Inclusion criteria (children)

We will include children, if they are

- Studying in year-five in the participating school and their age range is between 9 and 12 years
- Self-reported non-tobacco users (i.e. smoked or smokeless)

8.2 Exclusion criteria (children)

We will also exclude children, if they have any of the following conditions/situations that the school is aware of:

- Serious medical condition which is either life threatening or requires regular hospitalisation
- History of domestic violence and abuse (in any form)

We will include all consented children within classroom-based activities. We will, however, exclude children who are active smokers (either self reported or through a cotinine baseline test) or abuse victims by not including their data within the trial and by not sending any intervention related materials to their homes.

8.3 Identifying eligible participants (children)

We will request schools to prepare a list of eligible children including all those that meet the inclusion criteria and excluding those that fall into the exclusion criteria list. Once an eligibility list is prepared, we will give all schools the required number of trial information packs to proceed with the recruitment.

8.4 Consenting and enrolling participants (children)

All children participating in this trial will be under 16 and therefore parental/carer consent is required for them to take part. We will obtain parental consent on an opt-out basis, as follows. The participating schools will send out the trial information packs to parents of all eligible children, containing an information sheet, and a parent/carer opt-out consent form. We will ask parents/carers to discuss the trial with their child/children. If parents are not willing for their children to participate in the trial, we will ask parents to indicate this by either sending us an opt-out consent form in a self-addressed envelope or call/text/email us on the contact details provided within the information pack. If there are any queries, we will request parents to call/text/email us on the contact details provided within the information pack. We will give parents/carers a minimum period of seven days to indicate if they don't wish their children to take part in the study before sending them a reminder. If there is no indication from the parents that they do not wish their child to take part in the trial even after the reminder, we will assume parental consent. We used the same opt-out approach in CLASS II pilot trial after consulting with teachers and parents and faced no issues. It is also important to use opt-out consent for the wider societal benefit. In previous school-based studies, parents from relatively poor socio-economic backgrounds have been less engaged with school-based activities. In the

CLASS trial, when we used an opt-in approach, we were unable to recruit children from poor-socioeconomic backgrounds. With this concern of children from poor socio-economic backgrounds not recruiting and potentially benefiting from the trial, we used an opt-out approach in CLASS II trial and also propose to use this approach here. Without this approach, the researchers will fail in performing an important public task of including disadvantaged families in research and allowing them to benefit from it.

Moreover, at the time of recruitment, children will be of an age (9 to 12 years) where they are able to understand their potential involvement in research and can make an informed decision. Children will therefore be provided with an age appropriate information sheet, which will be given out to them at school. The children's Assent form will be administered within school at the same time when the trial information packs will be sent to the parents. The assent forms can be taken home to allow children to take their time in deciding and consult with their parents if they want to take part in the trial. If children are unwilling, they can either let their teachers or parents know, as they feel appropriate. If parents indicate their disapproval for their child to take part in the study, this will supersede the child's assent to participation. Any child who or whose parents/carers have declined to participate will be taken out from the list of eligible children by the school and the final list will be handed over to the research team. All participating children will be given an enrolment number (including a code for school), which will be recorded on the final list of eligible children, printed on all enquiry tools and entered in the database.

68 schools (34 in each country) and 2,720 children (1,360 in each country) will be recruited over a period of 18 months i.e. 12 months for recruitment and another 6 months contingency (see below). The recruitment will be staggered and each country will have a recruitment target of three schools and 110 children per month. In practice, a recruitment period of one week will be allocated to each school. We will secure expression of interest from eligible schools a month in advance of their allocated recruitment week. Two weeks prior to the recruitment week, our team will liaise with the respective school in preparing lists of eligible children and sending them and their parents the recruitment packs. This will ensure that all eligibility assessments and consents are in place prior to the recruitment week. Based on our experience in the feasibility studies (e.g. 12 schools were recruited in three months in CLASS II trial)[5], we are confident that our teams will meet these targets. However, we have added another six months to the trial recruitment period; this will not only cover summer holidays and exam periods, but will also provide contingency in case of school closures due to natural disasters and political instability; unfortunately both are common in Bangladesh and Pakistan.

8.5 Ineligible and non-consenting participants (children)

Those children who don't meet the eligibility criteria or those who meet the criteria but either their parents or they won't agree to participate after receiving the trial information, will not be enrolled in the trial. However, their reasons for not meeting the eligibility criteria or declining to participate will be recorded. This information will be kept completely anonymous.

8.6 Withdrawal of participants (children)

A child can be withdrawn from participation at any time even after enrolment or allocation. If a child is withdrawn from the intervention for any reason, their follow-up assessments and data collection will continue as per protocol unless parents/carers or children specifically ask for their withdrawal from the study completely. However, if the child is withdrawn completely from the study, then no more data will be collected. They will still be included in the analysis and counted as lost to follow

up. The information already collected will be kept in the database unless parents/carers or child specifically asks for their information to be removed.

While conducting our feasibility/pilot work on SFI, we were conscious of the potential for negative consequences of children raising concerns with their parents about adult smoking behaviours. However, both children and teachers reported no adverse events despite specific enquiries at the follow-ups.[5] In-depth qualitative interviews with school teachers also did not reveal any negative consequences. Despite this, we are putting a number of safe-guarding measures in place, which includes parental consent, sensitising schoolteachers to identify signs of distress resulting from children's interactions with their parents and encouraging children and parents to report their concerns. We will also keep a risk log to record and manage all the risks.

9. Cluster (schools) randomisation and allocation

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 (with a random element incorporated to help maintain allocation concealment). 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 ($B:G < 0.95$, $0.95 \leq B:G \leq 1.05$, $B:G > 1.05$) and the number (N) of students in year five at the participating school cluster ($N < 30$, $30 \leq N \leq 60$, $N > 60$). The minimisation will be implemented using the community contributed Stata command rct_minim. The first cluster will be allocated using simple randomisation, with minimisation used to allocate all subsequent clusters. To facilitate blinding (of the statistician), the statistician will use the minimisation algorithm to generate allocations to groups labelled A and B, with these being matched with the Intervention and Control conditions according to some pre-specified labelling known to the research teams in Bangladesh and Pakistan, but concealed from the statistician. Because of the nature of the intervention, it will not be possible to mask the children and schoolteachers from the allocated intervention. To avoid bias, we will ensure that all baseline data are collected before treatment allocation. Moreover, 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.

10. INTERVENTION DETAILS

Once children are enrolled, schools will be randomised to receive either the Smoke Free Intervention or treatment as usual. These treatment conditions are described as follows:

10.1 Smoke Free Intervention (SFI)

Through a number of small exploratory studies between 2010 and 2017, our team has gathered sufficient evidence for the feasibility of SFI in a range of settings. It was first tested in five schools in Leeds, UK,[15] and showed a rise in the proportion of smoke-free homes (self-reported) from 35% to 68%, post-intervention. Focus group discussions with children and parents conveyed acceptability of the intervention. The intervention was culturally adapted and tested in schools in Bangladesh and in Pakistan.[10 16] In Pakistan,[10] the adapted-SFI was found feasible and appropriate in a typical semi-rural setting. The proportion of smoke-free homes (self-reported) increased from 43% to 85% post-intervention. In Bangladesh,[16] the adapted-SFI was found acceptable and feasible in a study involving 24 schools. Compared to the control arm, the proportion of smoke-free homes (self-reported) increased and social visibility of smoking at home reduced significantly in the SFI arms. The above studies also showed that children were able to learn negotiation skills and develop

confidence in using these skills with their family. Moreover, boys and girls used different strategies to negotiate smoke-free homes with their parents. In a subsequent pilot trial (CLASS II)[17] of SFI vs. usual care, we used an objective measure for SHS exposure and found an encouraging difference in SHS exposure between the two arms. Our proposed trial (CLASS III) is the natural sequence, which follows the encouraging findings of the above studies and uses the MRC Framework for Developing and Evaluating Complex Interventions[18].

All participating children in the intervention arm will receive the SFI delivered by their teachers. Teachers will receive prior training in delivering the intervention. Their training will focus on their knowledge gaps around tobacco, their skills in using various teaching methods and their ability to build confidence within and teach negotiation skills to children.

The intervention will consist of:

- Two 45-minute sessions delivered over two days by schoolteachers. The duration of these sessions is consistent with regular school lessons. These sessions will consist of a flip chart presentation and a full drama activity. These activities are especially designed to increase pupil's knowledge about SHS and related harms, and motivate them to follow one main step (7 steps away from home) to make their home smoke free. The seven acts of the drama will give children the opportunity to practice their negotiating skills and be confident within their cultural context.It will also serve as a visual incentive for the parents not to smoke inside homes.
- A set of four follow-up sessions (15 minutes each) to reinforce key messages delivered in the initial sessions, to be delivered once a week over 6-7 weeks after the two initial sessions. The immediate first follow up session will be based on the feedback from parents about the drama activity. The second session will consist of a word search game followed by a discussion in order to enhance pupils' knowledge about SHS. The third follow up session will comprise a quiz game in which children will be asked questions and given answer options. This will be followed by a discussion as a means of reinforcement. The final follow up session will be based on small group discussions among the students about their experiences and if they faced any challenges.
- Children are given an achievement certificate to mark the seven achievements to make their homes smoke free. Children are also given a promise form that describes the main step to achieve smoke free home i.e to take seven steps away from the house to smoke. It also contains a tear-off slip to make a commitment to impose smoking restrictions at home. Children take promise forms to their parents, show them the messages, and negotiate with them to "sign-up" to the Smoke Free Homes "promise" form. One of the implications is that even if parents are non-smokers, they will not allow other smokers (residents and visitors) to smoke inside homes. In addition to delivering the intervention, teachers will also be trained to support children in this process.

Table 1: A logic model of the Smoke-Free Intervention (SFI)

Resources	Activities	Outputs (for process)	Short term outcomes	Medium term outcomes	Long term outcomes	Impact
Year-5 Schoolteachers Relevant resource materials Teacher training Teachers training to pick up any signs of distress among children as an untoward consequence of SFI. 2 x 45m sessions over two consecutive days	Storytelling, drama and role-play activities focused on building children's confidence in raising their concerns about SHS with their parents and enhance their negotiation skills, and allowed children to learn and practice relevant negotiating strategies. 1. Information about health consequences 2.Salience of consequences 3.Behavioural practice/rehearsal 4. Goal setting (behaviour)	Evidence of practicing strategies, developing skills and confidence around SHS negotiation. Evidence of knowledge of harms	SFH / SHS negotiation self-efficacy SFH / SHS negotiation intentions Evidence of knowledge of harms Knowledge MOA Intentions Skills Beliefs about consequences Knowledge	Self-reported smoking restrictions Salivary cotinine Adverse event monitoring: Distress arising from SRI	Frequency severity of respiratory symptoms Lung function tests	Academic Performance Questionnaire (APQ) School absenteeism Quality of life Health service use
Four refresher sessions (15 min each) over the subsequent 4 weeks.	The discussion, quiz, and games aimed to make children aware of the harms of SHS and motivate them to achieve a smoke-free home." Revising the salient points of the initial sessions encouraging children to share their experience of initiating relevant conversations within their families encouraging children to share their experience of initiating relevant conversations within their families Information about health consequences Salience of consequences Behavioural practice/rehearsal Goal setting (behaviour	Evidence of knowledge of harms of SHS from quiz answers Evidence of motivation to achieve SFH from games. Evidence of sharing relevant experiences of initiating conversations around SHS and SFH.	SHS Risk awareness, SHS Negative outcome expectancies SFH intentions. SFH / SHS negotiation self-efficacy SFH / SHS negotiation intentions MOA Knowledge Beliefs about consequences Intentions			
Home promise forms for Families (described in activities)	Reading of graphic representations of the hazards of SHS, pictorial guidance to help them make their homes smoke free, and a tear-off slip to commit to imposing smoking restrictions at home visitors & cars. 1.Goal setting (behaviour) 2 Problem solving 3. Action planning 4. behavioural contract	Evidence that the home promise form was taken home.	Action planning to negotiate SFH / SFH self-efficacy SFH intention MOA Intentions Beliefs about consequences Behavioural regulation Behavioural Cueing			

10.2 Treatment as Usual

Schools in the control arm will receive the intervention at the completion of the trial.

11. Outcomes assessments

A causal link between SHS exposure and respiratory infections is well established.[3] In the form of salivary cotinine, we also have a highly sensitive and specific biomarker of SHS exposure.[19] Therefore, we propose SHS exposure (proximal) and respiratory symptoms (distal) as the primary and secondary outcomes, respectively.

The outcomes for the definitive trial will also be measured before and after the intervention in each of the study's arms. We first describe these outcomes and then the process and schedule of assessing these (Table 2).

11.1 Primary outcome

Because of its very short half-life (2 hours), nicotine is not recommended as a useful measure of tobacco exposure.[2] 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.[2] Cotinine can be measured in various biological specimens including plasma, saliva, and urine. Using a threshold of 12ng/ml, salivary cotinine was found to have a 97% sensitivity and 97% specificity to detect tobacco exposure,[3] reducing the probability of false negatives and false positives to a minimum. Using the same threshold, salivary cotinine can also be used to detect those who don't use tobacco themselves but are exposed to SHS. Data from the Health Survey of England suggest that salivary cotinine above 0.5ng/ml, but less than the 12ng/ml threshold is due to SHS exposure; mean cotinine in those exposed to SHS was 1.99ng/ml.[4] Therefore, we intend to use children's salivary cotinine as a biomarker of SHS exposure (primary outcome). This was also successfully used in our CLASS II pilot trial.[5] Once children are enrolled in the study, saliva samples will be obtained from all participating children at baseline and also at 3-month post-intervention. Samples can be stored at ambient temperature for a period of two weeks before transported to a specialist laboratory - ABS Labs (https://www.abslabs.co.uk/) in the UK for it to be analysed using a gas-liquid chromatography technique. Samples will be sent in two batches at baseline and two at the first follow up. Samples will not contain any participant identifiable information and will only have the trial enrolment number. Their reports will be sent back to the central research office where these will be entered in the database.

11.2 Secondary outcomes

There will be a number of secondary outcomes, which are the same as we collected in the CLASS II pilot trial,[5] including the frequency and severity of respiratory symptoms, self-reported smoking restrictions, health service use, quality of life, academic performance, and school absenteeism. These will be measured at 3, 6 and 12 month follow ups (See table 2).

11.2.1 Frequency and severity of respiratory symptoms

For respiratory symptoms, children will be asked to keep a diary for 16 respiratory symptoms and record their severity on a validated four-point Likert scale[6] for a whole month (4 weeks) in three follow up periods i.e. 3rd, 6th and 12th month. For each item, '0' represents the absence of a symptom, 1 represents mild, 2 represents moderate and 3 represents the greatest severity level. For upper respiratory tract symptoms, children will report having a runny nose or sneezing, blocked or stuffy nose, sore throat or hoarse voice, headaches or face aches, aches or pains elsewhere, and feeling chill, fever, or shivers. For lower respiratory symptoms, cough on waking, wheeze on waking, cough during the day, wheeze during the day, shortness of breath during the day, night cough, and wheeze or shortness of breath during the night, will be included. For Otitis Media, hearing loss, drainage and pain in the ear will be recorded. Scores will be recorded daily and added up to give daily upper and lower respiratory-tract scores, respectively.

Symptom diaries will be printed and given to all participating children. The responses to all symptom items will be recorded by putting one out of four stickers in the given box. Facial expressions in the sticker will represent the four severity levels, described above. We propose to record symptoms for a whole month (4 weeks) in three followup periods i.e. 3rd, 6th and 12th month. Teachers will remind children at the start of each data collection week. At each follow up, data will also be recovered from the diary by the researchers and entered in the database. All children will provide data on section 1. However, only those children will provide data on section 2 and 3 whose cotinine levels are indicative of passive smoking at the baseline. Children will be told whether to stop or keep collecting information in their diaries in a letter.

11.2.2 Smoking related behaviours

We will ask the children to self-report levels of smoking restrictions and social visibility of smoking at home through a questionnaire. We will assess smoking restrictions using the following questions:

1).Do people who live with you smoke? (anywhere inside the house, in some rooms, only in one room, or only outside the house);

2). "Do people who visit your home smoke? (anywhere inside the house, in some rooms, only in one room, or only outside the house)".

We define 'open space outside house' as those spaces, which are still within house premises but not covered by a ceiling, such as, veranda, balcony, yard, garden, lawn, patio and open roof. Social visibility will be assessed by the following questions:

1). "Do people who live with you smoke in front of children?";

2). "Do people who visit your home smoke in front of children?"

For each outcome, the response categories across the two questions will be combined to form a composite variable (index) for analysis purposes.

Using the same questionnaire, we will also assess children's self-reported attitude towards smoking and intention to start smoking. We will use a five-point smoking uptake scale[21] to

categorise children as non-susceptible non-smokers, susceptible non-smokers, early experimenters, advanced experimenters and established smokers.

The above assessments will be carried out at both baseline and follow ups (Also see Table 2).

11.2.3 Health service use

We will use a health service utilisation questionnaire previously used in the pilot CLASS II and MCLASS trial,[23] to collect number and type of contacts with doctors, hospital admissions, pharmacy visits and antibiotic prescriptions. This information will be part of the baseline questionnaire but will also be assessed at all follow-up time points.

11.2.4 Quality of Life

Quality of life will be assessed using EQ-5D-Y questionnaire.[9] The questions will be included in the baseline and follow up questionnaires.

11.2.5 Other confounding variables

At baseline, we will also ask children to report on moderators of SHS risk for example smoking status of the cohabiting adults and a measure of SES based on the household assets. We will also inquire about some of the basic socio-demographic details on the questionnaire. These will include age, gender, overcrowding - number of rooms and residents, built environment, and tobacco points of sale in the house and school neighbourhoods,. Furthermore, we will include information on children's medical history (particularly asthma and chest infections) and use of any regular medications.

11.2.6 Absenteeism and academic performance

Each participating school will be asked to provide a report on the academic performance of participating children using the Academic Performance Questionnaire (APQ)[25] - This is a 10-item questionnaire to be completed by teachers. Using 4- and 5-point ordinal scales, it measures a child's performance in reading, mathematics, writing, and homework. This questionnaire will be completed at baseline and at all follow-ups. Furthermore, we will also use actual exam results (last term) in addition to APQ at the baseline and drop the latter if the actual exam results can be used as an outcome.

In addition, schools will also be requested to provide a record of child's absenteeism from school including the number of days missed every month in between two assessments.

Table 2: Table and schedule of assessments within CLASS III trial

Assessments	*Baseline*	*Post-intervention*

		Month 3	*Month 6*	*Month 12*
Eligibility and consent	X			
Socio-demographic & medical history				
-Personal details	X			
-Household details	X			
-Medical conditions and history of medications	X			
Smoking related behaviours				
-Smoking restrictions and social visibility	X	X	X	X
-Attitudes towards smoking	X	X	X	X
Health service use	X	X	X	X
Quality of life	X	X	X	X
Exposure to SHS – salivary cotinine	X	X		
-Respiratory symptoms diary		X	X	X
Academic assessment				
-Academic Performance Questionnaire	X	X	X	X
-School absenteeism report	X	X	X	X
Adverse event reporting		X	X	X
Process evaluation		X	X	

11.3 Data collection methods

Prior to randomisation, a baseline assessment will include a classroom administered questionnaire (including EQ-5D-Y, health service use and smoking behaviour) to be completed by participating children, APQ and school absenteeism form completed by schoolteachers and saliva sample collection by the research team for each child. Each child will also receive a respiratory symptoms diary with instructions on how to use it. Follow-up assessment will take place at three, six and 12 months post-randomisation involving only those children whose cotinine levels were indicative of SHS exposure at the baseline. In our pilot trial (CLASS II),[5] 95% of children were found to be exposed to SHS at baseline. Based on this, we expect to follow-up 95% of all children recruited in this trial. All assessments carried out at the baseline will be repeated at the follow-up assessment except cotinine levels which will only be assessed at month-three.

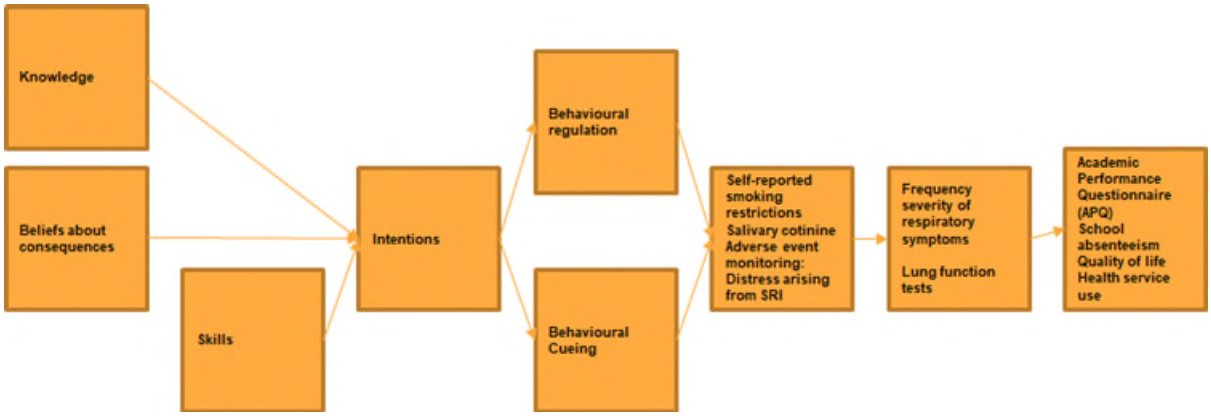
11.4 Process evaluation

A mixed-methods process evaluation will explore three key functions: mechanisms of impact, context and implementation.[14]

Mechanisms of impact (mediators and acceptability): All children will complete a short questionnaire at the 3- and 6-month follow-up, measuring mediators.The measurement strategy has been based upon the evidence for the links between the behaviour change techniques[26] that constitute the active ingredients of the intervention, and the respective mechanisms of actions of those techniques (see logic model and causal model). The evidence for these mediating constructs is drawn from three related studies [27,28,29] that utilised evidence synthesis and expert consensus to build the basis for the links. Additional work will be undertaken to operationalise these mechanisms of action, given the age of the participants, using established methods and scales, with a focus on ensuring cultural and contextual sensitivity.

For the knowledge construct, we plan to adapt the Smoking Attitudes Knowledge and Practice (S-KAP) Instrument (Knowledge Component)[30]. For the beliefs about consequences construct we will adapt the smoking related health-beliefs scale[31]. For the skills construct, we will adapt a behaviour specific self-efficacy scale[32]. For the intentions construct, we will adapt a behaviour-specific behavioural intentions scale[33]. For self-regulation, we will adapt the Goal-Setting Scale and Planning and Scheduling Scale[34]. For the behavioural cueing construct, we will adapt the Self-Report Habit Index[35].

Figure 2. Causal mechanisms for the intervention



In the 3-month questionnaire the children in the intervention arm will report which SFI activities they engaged with, acceptability of those activities and the perceived impact on smoking in their family home. At 3-month follow-up a focus group discussion with 6-8 children will be run in 6 (Bangladesh) and 6 (Pakistan) intervention arm schools (purposively selected whilst reflecting a mix of private/public and boys to girls ratio) to explore key issues that emerge from the questionnaire, for example the children's experiences of negotiating a SFH with their family.

Context: Contextual factors (e.g. socio-economic status) will be measured in for all children in the baseline, 3- and 6-month follow-up questionnaire (see section 11.2.5). In the 12 selected schools, the teachers and head teachers (2 and 1 per school respectively) will be interviewed once the SFI has been delivered. The interviews will explore how contextual factors such as the school environment and other social, economic, cultural, environmental and political factors have influenced the delivery and impact of the SFI. The focus groups with children and parents will explore how contextual factors such as the family environment have influenced the impact of the SFI. Around 6-8 parents whose children will be participating in the study will be invited to take part in a group discussion which would take approximately 60-90 minutes. The group discussion will be audio-recorded and analysed later in the study.

Implementation (feasibility, fidelity): The teacher/head-teacher interviews will also explore implementation issues including perceptions of the potential reach of SFI, likely obstacles and potential opportunities for scale up. Fidelity to delivering the six SFI sessions will be assessed using a fidelity index, linked to the behaviour change techniques that underpin the SFI, to assess intervention delivery adherence. All SFI sessions (in all schools) will be audio-recorded and a random sample of 10% of the sessions will be checked for fidelity using the index. We will ensure we include a mix of the six different sessions. To assess fidelity to the child-parent interaction we will use self-reported data from children captured in their achievement form (e.g. did they ask someone not to smoke in front of them, ask adults to put the smoking materials away, have the conversation with the adults/carers to make homes smoke-free). We will review the self-reported data collected from parents in the promise form to assess fidelity for committing to making their home smoke free and to smoke 7 steps away from the home.

We will also interview 2-3 policy makers in each country to explore their views on opportunities for implementing and scaling-up the SFI and how best to work with schools and policy makers to overcome the obstacles and maximise the opportunities.

The focus groups and face-to-face interviews will be conducted using a topic guide to ensure consistency, with flexibility to allow participants to generate naturalistic data on what they see as important. We will draw on the findings of the CLASS 2 (pilot study) process evaluation and relevant studies (e.g. a qualitative systematic review on the barriers and enablers to a smoke-free home[36] to ensure we include all potentially relevant issues in the topic guides (for all three process evaluation components). We will use a hermeneutics approach[37] which encourages participants to discuss features of the intervention to elicit data on their experience of its delivery/receipt.

With the participants' permission, the focus groups and interviews will be audio recorded digitally and transcribed verbatim. The quantitative questionnaire and intervention fidelity data will be analysed descriptively. Focus group and interview data will be analysed using the Framework approach. Integration of the datasets will be done using a 'triangulation protocol' [38].

11.5 Data Management

11.5.1 Description of the data

- *Type of study*

  This is a two-arm cluster randomised controlled trial (RCT) with embedded economic and process evaluations. The data generated from the study will provide answers to the following questions:

  - What is the effectiveness and cost-effectiveness of a school-based Smoke-Free Intervention (SFI) in reducing children's exposure to second-hand smoke (SHS)?
  - Can the SFI be implemented?
  - What are the mechanisms through which the SFI produces change and the contextual factors that influence the implementation and effectiveness of the SFI?
  - What are the likely obstacles to and opportunities for implementing and scaling-up the SFI and how is it best to work with schools and policy makers to overcome the obstacles and maximise the opportunities?

- *Types of data*

  The primary outcome will be SHS exposure (mean salivary cotinine measured at month 3) and secondary outcomes will be the frequency and severity of respiratory symptoms, self-reported smoking restrictions, health service use, quality of life, academic performance, and school absenteeism.

For respiratory symptoms, children will be asked to keep a diary for 13 respiratory symptoms and record their severity on a validated four-point for a whole month (4 weeks) in three follow up periods i.e. 3rd, 6th and 12th month.

Children will also report on smoking restrictions at home and its social visibility in children's environment both at home and outside. The questionnaire will ask: (i) " Do people who live with you smoke?" (Anywhere inside your home/in some rooms in your home/only in one room in your home/only outside); (ii) ''Do people who visit your home smoke?" (Anywhere inside your home/in some rooms in your home/ only in one room in your home/ only outside); (iii) "Do people who live with you smoke in front of children?" (Y/N); and (iv) 'Do people who visit your home smoke in front of children?' (Y/N).

Children's academic performance will be assessed using a 10-item 'Academic Performance Questionnaire' (APQ), and quality of life will be assessed using EQ-5D-Y questionnaire. We will also use a health service utilisation questionnaire.

For the process evaluation, focus group and questionnaire data on children's engagement with the SFI and mediators/moderators of intervention impact e.g. SHS risk awareness will be collected. Focus group data on parent's experience of the SFI, interview data on teachers/headteacher's experience of the SFI, and observation of delivery of the SFI will also be collected. Finally interview data on policy maker's views on scale-up will be collected.

Finally, the study will also generate economic data to estimate the cost of intervention. The economic evaluation plan is detailed in section 15.

- *Format and scale of the data*

The CLASS III trial will be conducted in 68 schools (34 schools each in Bangladesh and Pakistan with an average class size of 40 resulting in approximately 2,720 children in total – 1,360 in each arm). The field data collectors will collect trial data using mobile digital tablets. An online data tracker will help in monitoring timely data capture on all recruited participants. These processes will be trialled before the commencement of the trial. If not feasible then we will revert to collecting information in paper format. This will then be entered into a database at the University of York on a secured server. All the data will be transferred to the statistician in York who will conduct the analysis using the statistical software packages: STATA and R.

The process evaluation will be conducted in 12 schools (6 in Bangladesh, 6 in Pakistan). Qualitative interview (n=36 teachers/headteachers, 4-6 policy makers) and focus group (n=24 focus groups with children, and 24 focus groups with parents) data will be collected using digital recorders and transferred to the secure computer of the local qualitative researcher, to be analysed using NVivo and Excel. All SFI sessions will be audio-recorded and the data transferred as for the interviews/focus groups. Researchers will complete the fidelity index in Excel. .

11.5.2 Data collection/generation

- *Methods for data collection/generation*

All participating schools will compile a list of eligible children who will then be recruited after obtaining written, informed, assent and parental consent. Soon after obtaining

assent and parental consent, we will carry out children's baseline assessments and record their socio-demographic details and medical history. Other baseline measurements will include: salivary cotinine levels; smoking related behaviours; health service use; quality of life; and academic assessment. These will also be measured at the three follow-ups, in addition, to adverse events. The saliva samples will be collected by keeping a sterile swab in the mouth for approximately five minutes and then transfer to a sterile plastic container.

Focus groups with children and parents will occur at 3-month follow up. Interviews with teachers/headteachers and policy makers will occur once SFI delivery is completed. Quantitative process evaluation data from the children will be collected in the 3- and 6-month follow-up. Fidelity data will be collected during SFI delivery.

- *Data quality and standards*

For saliva sample quality measurements, samples will be stored for a maximum period of two weeks before being transported to a specialist laboratory in the UK. We have used these processes successfully in CLASS II. Overall data quality will be ensured through training and supervision. Data entry validation will occur by double-checking a random sample of the data in the field. Moreover, quantitative data once entered will also be peer-reviewed by the statistician.

The quality of the qualitative interview /focus group data will be ensured by training the qualitative researchers in Bangladesh and Pakistan and through detailed feedback from a senior qualitative researcher in York on the first few transcripts to ensure good interview/focus group facilitation technique. In all steps of the data analysis, rigorous procedures to ensure "trustworthiness" of the findings will be undertaken – the coding framework will be produced as a team, a 10% sub-sample of the coding of the transcripts will be checked, and a sample of sections of the analysis write up will be jointly produced (with the senior researcher in York). Thematic frameworks will be shared and discussed across the partner organisations to ensure credibility.

11.5.3 Data management, documentation and curation

- *Managing, storing and curating data*

If data is collected in paper form, then it will be stored in the research offices in Bangladesh and Pakistan in a cupboard under lock and key. All consent forms will be secured safely in a separate locker. Electronic data will be entered into a secure server protected by a password and only accessible to the data entry officer, trial coordinator, and the trial statisticians.

The interview focus group and SFI intervention delivery (for fidelity assessment)data will be collected on a digital audio recorder. On return to the office, the recording will be immediately transferred to a secure, password-protected server. The digital recorder will be stored in a locked cupboard. Once the interview/focus group has been transcribed and checked, and the SFI session has been assessed for fidelity the recording will be deleted off the digital recorder. It will be deleted from the server once

the data analysis is completed. Transcriptions and fidelity indices will be stored on the secure server.

- *Metadata standards and data documentation*

  We will keep a file describing the data we have created and what measurements were used to obtain the data at each time point. This will be in the form of a 'Data Dictionary', which will be based on standard templates. There will be a separate template for each variable; the Study Management Teams will complete these, as they collect the data.

- *Data preservation strategy and standards*

  Once data is entered into a secure server and anonymised, it will be shared with the University of York where it will be analysed. Data will be stored for a period of ten years as per University's policy.

11.5.4 Data security and confidentiality of potentially disclosive information

- *Formal information/data security standards*

  Ethics Authority approval will be obtained from the University of York's Health Sciences Research Governance Committee (HSRGC) before the study commences. Approval will also be obtained from the necessary authorities in Bangladesh and Pakistan.

  Data management will comply with the Data Protection Act (2018) and the General Data Protection Regulations (GDPR). https://www.york.ac.uk/records-management/dp/. Each participant will be asked to understand and sign an approved consent form, before they take part in the CLASS III study. Parental consent will be sought prior to children taking part. Data collected using questionnaires and interviews/focus groups will be pseudo-anonymised to remove information, which could identify the participant. Completed paper questionnaires (if applicable), consent forms, recordings and transcripts will be kept inside a locked cabinet in the relevant office. Electronic data will be collected on password-protected devices. Data will be transferred securely to the database, which will be installed on a secure server (password-protected). Audio recordings will only be listened to by members of the research team. All documents and audio recordings will be retained for a minimum of 5 years and then destroyed, according to University of York policy.

- *Main risks to data security*

  Trial data collected carries a risk of breach in participant confidentiality. Linking research data with the participant will only be possible though linking study ID number to the personal information in the consent form. Consent forms will be stored separately from the paper questionnaires (if applicable) in the research office in Bangladesh and Pakistan in a safe locked cabinet. Only trial coordinators and PI will have access to these. Participants will not be identified in any public reports or documents. In case manual data entry is required, this will be carried on designated password-protected computers at the research office in each country and will be backed up daily. All data will be stored and transferred following HIPAA protocol. The study personnel will receive training on data protection. Study personnel will be monitored to ensure compliance with the privacy standards.

11.5.5 Data sharing and access

- *Suitability for sharing*

  Once anonymised, data will only be shared between research offices in Bangladesh and Pakistan using a secure server and University of York.

- *Discovery by potential users of the research data*

  Not applicable

- *Governance of access*

  Not applicable

- *The study team's exclusive use of the data*

  Once we have completed the analysis and published all intended scientific journals, we will make our data available for other researchers.

- *Restrictions or delays to sharing, with planned actions to limit such restrictions*

  Not applicable

- *Regulation of responsibilities of users*

  Not applicable

11.5.6 Responsibilities

Data protection/management officer at the department of Health Sciences, University of York

11.5.7 Relevant institutional, departmental or study policies on data sharing and data security

Policy	URL or Reference
Data Security Policy	http://www.york.ac.uk/records-management/dp/policy/
Data Sharing Policy	*http://www.york.ac.uk/library/infofor/researchers/data/sharing/*
Institutional Information Policy	*http://www.york.ac.uk/about/departments/support-andadmin/information-directorate/information-policy/*

12. ADVERSE EVENTS PROCEDURES

We are expecting a minimal number of adverse and no serious adverse events during the study. SFI is an educational intervention and has been very well received in our previous studies without leading to any directly related adverse events. Nevertheless, there will be a vigilant surveillance system in place for adverse events occurring during the course of the trial with particular emphasis on identifying, recording, reporting and managing any serious adverse events. We will sensitise school teachers to look for signs of any adverse events resulting from the interactions between children and their parents. We will also encourage children and parents to report any related adversities.

12.1 Definitions

12.1.1 Adverse event (AE)

An adverse event is any untoward clinical event in a trial participant, which may or may not be related to the study intervention. The clinical event could be unfavourable and unintended symptom, sign, medical condition, abnormality, or disability that has appeared or worsened during the course of the trial, regardless of a causal relationship to the study intervention.

12.1.2 Serious Adverse Event (SAE)

A serious adverse event is any clinical occurrence that:

- Results in death of the participant
- Is life threatening, defined as an event in which the participant is at risk of death during the event. This does not refer to incidents that hypothetically might have led to death if the event worsened.
- Results in hospitalisation or prolongation of hospital stay
- Results in persistent and/or significant disability and/or incapacity
- Birth defect or congenital anomaly
- Any medical condition that may not be life threatening, disabling or resulting in hospitalisation but requiring medical or surgical intervention to prevent one of the above outcomes

Please note that any planned surgery or medical procedure will not be considered as an SAE

12.2 Detecting, recording, and reporting of AEs and SAEs

In the event of any adverse event reported by the child, their parents/carers, or school teachers, research assistants will complete an adverse event form, which will include medical diagnosis, if relevant and available. The Research Assistant will also call the trial manager on the same day providing a verbal report of the event. The trial manager will ensure that the event is classified appropriately after receiving the verbal report. All AEs will be reported to the Principal Investigators (Bangladesh and Pakistan) within three days of detection. AE data will be collated and reported to the trial sponsors and National Bioethics Committee at six-monthly intervals. These must also be reported to the Study Operational Committee and the Independent Trial Steering Committee at their regular meeting. All AEs that have the potential to develop into SAEs will be followed to resolution or stabilisation and reported as SAEs if they become serious. All SAEs must be reported to the Principal Investigator within 24 hours of detection and should also be reported to the trial sponsors and National Bioethics Committee within three working days. All serious events must also be reported to all study investigators and the chair of the Independent Trial Steering Committee within three days. The Chief Investigator will have the overall responsibility to ensure that all adverse events are reported according to the above protocol.

12.3 Evaluation of AEs and SAEs

In addition to assessing seriousness, the trial manager will assess all AE for causality, severity, and expectedness.

12.3.1 Assessment of causality and relatedness

This will be done in consultation with the Principal Investigator and the event will be classified as follows:

Unrelated: When the event is considered not related to the study intervention

Possibly: When an association of the event with the study treatment cannot be ruled out

Probably: When temporal association and an absence of any other explanation suggest that the event could be related to the study intervention

Definitely: Evidence suggests that the study intervention is the most likely cause of the event

12.3.2 Assessment of severity

Trial Manager can make the following assessment based on severity, which should not be confused with seriousness (a statutory definition) differentiating between AEs and SAEs.

Mild: These events cause minimal discomfort, easily tolerated and do not interfere with routine life activities.

Moderate: These events cause moderate discomfort and do interfere with routine life activities.

Severe: These events cause much discomfort and lead participants to stop their routine life activities.

12.3.3 Assessment of expectedness

If the event is judged an adverse reaction, serious or otherwise, must be judged on expectedness based on what is already known about the intervention under study.

12.4 Follow-up procedures

These events will be followed up until resolution or returning to a stable medical state. We won't expect any events to be relevant to the trial that occur after the completion of follow up and therefore no active surveillance will continue beyond trial completion. Nevertheless, any event reported to the trial manager will be recorded and kept in the records along with other trial data.

13. STATISTICAL CONSIDERATIONS

13.1 Sample Size

Informed by the results of the CLASS-II trial, 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 0.05ng/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 of 0.4 and

intra-cluster correlation of 0.05, 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 (against 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).

14. STATISTICAL ANALYSIS

We will compare the average cotinine levels between the groups using a linear multilevel model controlling for pertinent baseline covariates (at the child and school level), minimisation factors and adjusting for clustering by schools. The distributional assumptions will be checked and different link functions (e.g., log link) will be considered. We do not plan to carry interim analyses. The main analysis will be carried out once at the end of the study. This will be conducted by the trial statistician who will be blinded to the treatment allocations. Checks for the data quality and completion rates will be carried out on a regular basis.

15. ECONOMIC EVALUATION

We will undertake a full cost-effectiveness analysis using methods that have already been piloted.[5] The first stage estimates the cost of delivering the intervention. Intervention costs will include the time and resources needed to deliver SFI. We will use the unit cost of the schoolteachers' time to compute the cost of delivering the sessions. Staff costs will be added to materials costs. We will present the estimated costs associated with delivery in each of the study sites, on a total and a per participant basis. Given that SFI is being delivered by the education sector we will present costs in a disaggregated form so that various perspectives can be used by decision-makers.

We will also use a service use questionnaire to record utilisation of health care resources, developed from the questionnaire used in the pilot. These include doctor and hospital visits for the treatment of childhood conditions related to SHS exposure and also medications dispensed for these illnesses with costs collected based on setting (Non-Governmental Organisations (NGOs), private and public). The self-administered questionnaire will be completed by pupils.

Total costs will include the costs of SFI as outlined above and wider health care costs including doctor and hospital visits for childhood illness related to second-hand smoke, (such as asthma, wheezing, middle ear infections, respiratory tract infections and meningitis). We will also record and calculate the costs of medications related to these illnesses, which are dispensed. Quantities of resource use (contacts) are multiplied by local unit costs to derive an individual cost profile. We will use published data to estimate the total cost attributable to second-hand smoking.

We will measure health related quality of life in children by using the EQ-5D-Y,[9] administered at baseline and each follow up period. The results will be used to calculate Quality-Adjusted Life Years (QALYs) for children in the trial. In addition, the symptoms for lower respiratory

infection and Otitis Media collected in the symptom diary will be used to estimate Disability Adjusted Life Years (DALY) changes for all children in the trial.

We will conduct an incremental cost-effectiveness ratio (ICER) analysis of SFI over and above the control. Costs and QALYs will be combined to calculate the incremental cost per QALY gain. We will also use multiple imputation techniques to assess the impact of missing data and construct cost-effectiveness acceptability curves to demonstrate the effect of uncertainty.

We also agree with the potential for a further proposal that would enable long-term projection of costs and outcomes and thus cost-effectiveness.

We will look at the potential costs that would be required to roll out SFI in a local health service setting based upon the costs calculated for SFI within the trial. This provides evidence of the scale of the budget that would be required to deliver the programme across a wider population.

16. PROJECT PLAN

This is a three and a half year project. We will recruit the necessary staff, secure approvals and expression of interest from schools in the first six months. We will recruit participants (schools and children), conduct baseline assessments and randomise schools to the trial arms in the following 18 months (12 months recruitment + 6 months contingency). Given that we recruited 12 schools in three months in the CLASS II pilot trial, we are confident in our ability to recruit 66 schools in 12 months (maximum 18 months) in Bangladesh and Pakistan, respectively. By month 24, we will complete all recruitment, baseline assessments and randomisation (minimisation)/ treatment allocation. Follow-ups will be staggered accordingly and are expected to be completed by month 36. We will complete the analysis in the next three months and dissemination activities (including writing manuscripts) over the following three months.

17. STUDY ORGANISATIONAL STRUCTURES

Our team has so far managed six trials in Bangladesh and Pakistan to completion, recruiting >7,000 participants. Our trial management relies on: (a) a **trial coordination team** (York) consisting of a trial coordinator, methodologist, statistician, qualitative researcher and an economist; (b) **York Trials Unit** (YTU) providing methodological, statistical and data management support; and (c) **trial and data management teams** (Bangladesh and Pakistan) consisting of trial manager(s), research assistants, field data collectors and data entry operators.

This will involve managing five critical aspects of the trial: (i) recruitment and retention; (ii) randomisation; (iii) data capture and quality; (iv) treatment delivery and adherence; and (v) adverse events. **Recruitment and retention:** The trial managers and research assistants will recruit the clusters and participants, respectively. The recruitment and retention will be monitored via an online trial recruitment tracker and reported on a weekly basis to the trial coordinator (York) at the trial coordination meetings. These will be compared against recruitment targets and reported back to the trial management committee on a bi-monthly

basis. **Randomisation:** Once a month, the trial management teams will provide key non-identifiable information on recruited clusters to the trial statistician based at YTU. Post-randomisation, the statistician will allocate these clusters to the two trial arms. **Data capture and quality:** The field data collectors will collect trial data using mobile digital tablets. An online data tracker will help in monitoring timely data capture on all recruited participants. Data quality will be ensured through built-in checks and through validation enquiries instigated first by the research assistants and then by the trial managers. All data queries will be handled first by the trial coordinator and then by the statistician. A data query log will be maintained throughout the trial. **Treatment delivery and adherence:** Once allocated, the trial managers will schedule intervention delivery at the respective schools on a monthly basis. A treatment compliance report will be presented at both weekly and bi-monthly meetings. **Adverse events:** All serious adverse events will be cascaded urgently as per protocol. All non-serious adverse events will be reported at both weekly and bi-monthly meetings.

The **trial coordinator** (York) will organise day-to-day trial activities, chair weekly trial coordination meetings and report bi-monthly to the trial management committee. She will supervise the two **trial coordinators (site-specific)** in Bangladesh and Pakistan. The trial coordinators (site-specific) will be responsible for clusters/participants recruitment and retention, data management, treatment as per allocation and adverse events management. Both will report to the trial coordinator (York) at the weekly trial coordination meetings. Their duties will include the supervision and monitoring of the local trial and data management teams. **Senior research assistants** will assess eligibility, consent and recruit participants. They will be responsible for all logistic arrangements within schools including the provision of intervention materials and saliva collection kits. They will work closely with **data collectors** who will be responsible for accurate and timely data collection at both cluster and individual levels. **Data entry operators** will ensure that all data entries are accurate and up-to-date. The **trial statisticians** will prepare a statistical analysis plan, respond to data queries, run validation checks and conduct the analysis. A **trial economist** will ensure economic data is collected accurately and timely and run the economic analysis. In addition, we will also hire **research associates** for recruitment and data collection for the process evaluation.

17.1 The Trial Management Group (TMG)

The TMG will consist of all study investigators and will be responsible for the delivery of the project. The committee will meet every fourth Wednesday every other month over SKYPE and will review trial progress, respond to any concerns raised by the trial manager and the principal investigator, propose remedial actions, and detect any forthcoming problems.

17.2 Independent Trial Steering Committee

An Independent Trial Steering Committee (ITSC) will be set up and will include an independent chair, at least two other independent members, chief investigator, research fellow, trial manager, trial statistician, and the principal investigator. The ITSC is likely to meet every six months but the Committee will decide on the frequency of meetings. The committee will oversee the trial and ensure that the trial is conducted according to the protocol and within the underlying ethical framework. Members will also provide advice outside these meetings according to their area of expertise at key stages via email, phone or if needed, face-to-face.

18. PROTOCOL AMENDMENT

All amendments to the protocol will be first discussed with the Chief Investigator and then submitted to the Bioethics Committee for formal approval. A judgement will be made on the nature of amendment i.e. major or minor as per guidance from the Bioethics committee. All minor amendments will be implemented once notified to the Bioethics Committee and all major amendments will be implemented once approved by the Bioethics committee.

19. PROTOCOL VIOLATIONS AND DEVIATIONS

Research team will not deviate from the protocol without agreement with the Chief Investigator and securing an agreement with the Bioethics committee and Study Operational Committee except in situations where a deviation is necessary to remove an immediate hazard to the participants. Any such deviations (both nature and reason) should be recorded in the adverse event form and if necessary an amendment to the protocol must be secured through formal process.

20. QUALITY ASSURANCE

The study will be conducted in accordance with current MRC Good Clinical Practice guidelines and the NHS Research Governance Framework. Administrative approval will be sought from each participating school. The study will be subject to all research management and governance procedures in place at the University of York, including the requirement for audit.

21. ETHICAL

The trial will be conducted to protect the human rights and dignity of the participants as reflected in the 1996 version of the Helsinki Declaration. Participants will not receive any financial inducement to participate in the trial. In order to protect the trial participants the following provisions will be made/upheld; the trial has been designed to minimise the burden of participants and any foreseeable risk in relation to the intervention involved; the explicit wishes of the participant will be respected, including the right to withdraw from the trial at any time; the interest of the participant will prevail over those of science and society; provision will be made for indemnity by the investigator and sponsor.

We will seek ethical approval from the University of York and Bangladesh and Pakistan Medical Research Councils, respectively.

Some of the ethical concerns are as follows: (a) Children's participation raises issues around competence, vulnerability and powerlessness. In this study, children's wishes and their welfare will take precedence over the research requirements. Research burden will be kept to a minimum; (b) Children and their families will not be reimbursed financially, however, small incentives in the form of school stationery will be offered; (c) Based on our feasibility work, it is highly unlikely that the children will face any adverse reaction from their families. Obtaining saliva is also not harmful to children, neither it could disclose the presence of any medical

condition; and (d) all participants' data will be kept confidential and in password protected servers.

22. STATEMENT OF INDEMNITY

The University of York is going to sponsor this trial and the University will be liable for negligent harm caused by the design of the trial.

23. DISSEMINATION

The issue of SHS is already a national priority in Bangladesh and Pakistan. If SFI is found to be effective, we will use advocacy, our existing linkages, and impact enhancement schemes to maximise the impact of our results (see below) in these countries and beyond. Priority: Widespread SHS exposure in women and children and its impact has recently caught public and policy makers' attention in Bangladesh and Pakistan. Two of our team's recent papers on the topic were reported widely in national newspapers and TV channels.[21,22] The Bangladesh government has responded by promising to prioritise this issue. Advocacy: We have partnered with NGOs within the two countries with expertise in advocating for tobacco control measures. Together, we will develop a dissemination strategy, which will target academic and non-academic audiences using a variety of media. In Bangladesh, our partner Work for a Better Bangladesh Trust has an expert advocacy team in reducing SHS exposure. In Pakistan, we are in liaison with the Director of Schools office within the Ministry of Education in Sindh, Pakistan who have extended their advocacy support. Partnerships: Since its adaptation and piloting in the CLASS II trial, policymakers at the ministry and the WHO have shown a keen interest in the intervention and have been kept engaged through stakeholder events and policy briefs. Beyond the two countries, our team is also connected to international funders and agencies supporting tobacco control efforts. These include the Global Alliance against Chronic Diseases (co-chair of the respiratory group), The Union (office bearers within tobacco control section), WHO Geneva, EMRO and SEARO offices and WHO FCTC secretariat (through existing partnerships - EU-H2020 TB & Tobacco consortium, NIHR_RESPIRE Unit and NIHR_ ASTRA Group). We will use these partnerships to disseminate and seek support for our research findings. Impact enhancement: Our team is currently leading a NIHR Global Health Unit (RESPIRE) and a Group (ASTRA), both based in south-east Asia. This gives us the opportunity to enhance our trial's impact through our interface with relevant policymakers, professional bodies and third sector organisations, and also to extend this work to other countries such as India and Malaysia in due course. Through GCRF and ESRC schemes, we have been successful in securing grants to enhance the impact of our research recently (TB & Tobacco *plus*). We use these schemes to demonstrate scale-up beyond trial sites and generate useful knowledge and momentum for a national scale-up. We will apply for these schemes towards the end of the CLASS III trial. We will also partner with governments and NGOs to seek implementation grants from funders like World Bank for a national/provincial roll-out. We will also support governments' funding mechanisms (e.g. PC1 in Pakistan) to support scale-up.

24. REFERENCES

1. World Health Organization. WHO report on the global tobacco epidemic, 2017: Monitoring tobacco use and prevention policies. Geneva: World Health Organization, 2017.

2. Oberg M, Jaakkola MS, Woodward A, et al. Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. *Lancet (London, England)* 2011;377(9760):139-46. doi: 10.1016/s0140-6736(10)61388-8 [published Online First: 2010/11/30]

3. Cook DG, Strachan DP. Health effects of passive smoking: Summary of effects of parental smoking on the respiratory health of children and implications for research. *Thorax* 1999;54(4):357-66.

4. Burr ML, Anderson HR, Austin JB, et al. Respiratory symptoms and home environment in children: a national survey. *Thorax* 1999;54(1):27-32.

5. Chen R, Clifford A, Lang L, et al. Is exposure to secondhand smoke associated with cognitive parameters of children and adolescents?--a systematic literature review. *Ann Epidemiol* 2013;23(10):652-61. doi: 10.1016/j.annepidem.2013.07.001 [published Online First: 2013/08/19]

6. Consortium PHR. A review of young people and smoking in England. London, 2009.

7. Reece S, Morgan C, Parascandola M, et al. Secondhand smoke exposure during pregnancy: a cross-sectional analysis of data from Demographic and Health Survey from 30 low-income and middle-income countries. *Tob Control* 2018 doi: 10.1136/tobaccocontrol-2018-054288 [published Online First: 2018/07/22]

8. Shah S, Kanaan M, Huque R, et al. Secondhand Smoke Exposure in Primary School Children: A Survey in Dhaka, Bangladesh. *Nicotine & Tobacco Research* 2017:ntx248-ntx48. doi: 10.1093/ntr/ntx248

9. Wille N. Badia X. Bonsel G. et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. Qual Life Res. 2010; 19: 875-886

10. Siddiqi K, Sarmad R, Usmani RA, et al. Smoke-free homes: an intervention to reduce second-hand smoke exposure in households. *Int J Tuberc Lung Dis* 2010;14(10):1336-41.

11. Siddiqi K, Khan A, Ahmad M, et al. Action to stop smoking in suspected tuberculosis (ASSIST) in Pakistan: a cluster randomized, controlled trial. *Ann Intern Med* 2013;158(9):667-75. doi: 10.7326/0003-4819-158-9-201305070-00006

12. Behbod, B.; Sharma, M.; Baxi, R.; Roseby, R.; Webster, P. Family and carer smoking control programmes for reducing children's exposure to environmental tobacco smoke. Cochrane Database Syst. Rev. 2018, 31, CD001746.

13. Daly JB, Mackenzie LJ, Freund M, et al. Interventions by Health Care Professionals Who Provide Routine Child Health Care to Reduce Tobacco Smoke Exposure in Children: A Review and Meta-analysis. *JAMA Pediatr* 2016;170(2):138-47. doi: 10.1001/jamapediatrics.2015.3342

14. Rosen LJ, Myers V, Winickoff JP, et al. Effectiveness of Interventions to Reduce Tobacco Smoke Pollution in Homes: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health* 2015;12(12):16043-59. doi: 10.3390/ijerph121215038 [published Online First: 2015/12/18]

15. Alwan N, Siddiqi K, Thomson H, et al. Can a community-based 'smoke-free homes' intervention persuade families to apply smoking restrictions at homes? *J Public Health (Oxf)* 2011;33(1):48-54. doi: 10.1093/pubmed/fdq073 [published Online First: 2010/10/07]

16. Huque R, Dogar O, Cameron I, et al. Children Learning About Second-Hand Smoking: A Feasibility Cluster Randomized Controlled Trial. *Nicotine Tob Res* 2015;17(12):1465-72. doi: 10.1093/ntr/ntv015 [published Online First: 2015/01/29]

17. Siddiqi K, Huque R, Kanaan M, et al. Children Learning About Second-hand Smoke (CLASS II): a pilot cluster randomised controlled trial. *Nicotine Tob Res* 2018 doi: 10.1093/ntr/nty090 [published Online First: 2018/05/18]

18. Verification SSoB. Biochemical verification of tobacco use and cessation. *Nicotine Tob Res* 2002;4(2):149-59. doi: 10.1080/14622200210123581

19.Medical Research Council. Developing and evaluating complex interventions: new guidance. London: Medical Research Council; 2008.

20. Chauhan AJ, Inskip HM, Linaker CH, et al. Personal exposure to nitrogen dioxide (NO2) and the severity of virus-induced asthma in children. *Lancet* 2003;361(9373):1939-44. [published Online First: 2003/06/13]

21. Consortium BC. Spirometry in practice: A practical guide to using spirometry in primary care. London: British Thoracic Society, 2005.

22. Ruge J, Ulbricht S, Schumann A, et al. Intention to quit smoking: is the partner's smoking status associated with the smoker's intention to quit? *Int J BehavMed* 2008;15(4):328-35.

23. Ainsworth H, Shah S, Ahmed F, et al. Muslim communities learning about second-hand smoke (MCLASS): study protocol for a pilot cluster randomised controlled trial. *Trials* 2013;14(1):295. doi: 10.1186/1745-6215-14-295

24. Rajmil L, Herdman M, Fernandez de Sanmamed M-J, et al. Generic health-related quality of life instruments in children and adolescents: a qualitative analysis of content. *Journal of Adolescent Health* 2004;34(1):37-45. doi: doi: DOI: 10.1016/S1054-139X(03)00249-0

25. Bennett AE, Power TJ, Eiraldi RB, et al. Identifying Learning Problems in Children Evaluated for ADHD: The Academic Performance Questionnaire. *Pediatrics* 2009;124(4):e633-e39. doi: 10.1542/peds.2009-0143

26. Michie, S., Richardson, M., Johnston, M., Abraham, C., Francis, J., Hardeman, W., ... & Wood, C. E. (2013). The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Annals of behavioral medicine*, *46*(1), 81-95.

27. Connell, L. E., Carey, R. N., de Bruin, M., Rothman, A. J., Johnston, M., Kelly, M. P., & Michie, S. (2019). Links between behavior change techniques and mechanisms of action: an expert consensus study. *Annals of Behavioral Medicine*, *53*(8), 708-720.

28. Carey, R. N., Connell, L. E., Johnston, M., Rothman, A. J., de Bruin, M., Kelly, M. P., & Michie, S. (2019). Behavior change techniques and their mechanisms of action: a synthesis of links described in published intervention literature. *Annals of Behavioral Medicine*, *53*(8), 693-707.

29. Johnston, M., Carey, R., Bohlen, L. C., Johnston, D. W., Rothman, A., de Bruin, M., ... & Michie, S. (2018). Linking behavior change techniques and mechanisms of action: triangulation of findings from literature synthesis and expert consensus.

30. Delucchi, K. L., Tajima, B., & Guydish, J. (2009). Development of the smoking knowledge, attitudes, and practices (S-KAP) instrument. Journal of drug issues, 39(2), 347-363.

31. Kaufman, A. R., Koblitz, A. R., Persoskie, A., Ferrer, R. A., Klein, W. M., Dwyer, L. A., & Park, E. R. (2015). Factor structure and stability of smoking-related health beliefs in the National Lung Screening Trial. Nicotine & Tobacco Research, 18(3), 321-329.

32. Wilson, K. E., Harden, S. M., Almeida, F. A., You, W., Hill, J. L., Goessl, C., & Estabrooks, P. A. (2016). Brief self-efficacy scales for use in weight-loss trials: Preliminary evidence of validity. Psychological Assessment, 28(10), 1255-1264.

33. Couraeya, K. S., & McAuley, E. (1993). Predicting physical activity from intention: Conceptual and methodological issues. Journal of Sport and Exercise Psychology, 15(1), 50-62.

34.Rovniak, L. S., Anderson, E. S., Winett, R. A., & Stephens, R. S. (2002). Social cognitive determinants of physical activity in young adults: a prospective structural equation analysis. Annals of behavioral medicine, 24(2), 149-156.

35. Verplanken, B., & Orbell, S. (2003). Reflections on past behavior: a self-report index of habit strength 1. Journal of applied social psychology, 33(6), 1313-1330.

36. Passey ME, Longman JM, Robinson J, Wiggers J, Jones LL. Smoke-free homes: what are the barriers, motivators and enablers? A qualitative systematic review and thematic synthesis. BMJ open. 2016 Mar 1;6(3):e010260.

37. Thirsk LM, Clark AM. Using Qualitative Research for Complex Interventions:The Contributions of Hermeneutics. International Journal of Qualitative Methods 2017; 16(1): 1609406917721068.

38. Farmer, T., Robinson, K., Elliott, SJ, Eyles, J. Developing and Implementing a Triangulation Protocol for Qualitative Health Research. Qualitative Health Research. 2006; 16(3), 377–394. https://doi.org/10.1177/1049732305285708