

Running head: cRCT of e-cigarettes

Evaluating the effectiveness of e-cigarettes compared with usual care for smoking cessation when offered to smokers at homeless centres: Protocol for a multi-centre cluster randomised controlled trial in Great Britain

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Abstract

Background and aims: Smoking is extremely common among adults experiencing homelessness but there is lack of evidence for treatment efficacy. E-cigarettes are an effective quit aid, but they have not been widely tested in smokers with complex health and social needs. Here we build on our cluster feasibility trial and evaluate the offer of an e-cigarette or usual care to smokers accessing a homeless centre.

Design: Multi-centre two-arm cluster randomised controlled trial with mixed-method embedded process and economic evaluation.

Setting: Homeless centres in England, Scotland and Wales.

Participants: Adult smokers (18+ years; $n= 480$) accessing homeless centres and who are known to centre staff and willing to consent.

Intervention and comparator: Clusters ($n=32$) will be randomised to either an e-cigarette starter pack with weekly allocations of nicotine containing e-liquid for 4-weeks (choice of flavours (menthol, fruit and tobacco) and strengths 12 mg/mL and 18mg/mL), or the usual care intervention which comprises very brief advice and a leaflet signposting to the local stop smoking service.

Measurements: The primary outcome is 24-week sustained CO validated smoking cessation (Russell Standard defined, intention-to-treat analysis). Secondary outcomes: i) Fifty percent smoking reduction (cigarettes per day) from baseline to 24 weeks; ii) 7-day point prevalence quit rates at 4-, 12- and 24-week follow-up; iii) changes in risky smoking practices (e.g. sharing cigarettes, smoking discarded cigarettes) from baseline to 4-, 12- and 24-weeks; iv) cost-effectiveness of the intervention; v) fidelity of intervention implementation; mechanisms of change; contextual influences and sustainability.

Comments: This is the first study to randomly assign smokers experiencing homelessness to an e-cigarette and usual care intervention to measure smoking abstinence with embedded process and economic evaluations. If effective, the results will be used to inform the larger scale implementation of offering e-cigarettes across homeless centres to aid smoking cessation.

Keywords: Smoking; homelessness; tobacco; e-cigarettes; vaping; ENDS; cessation; harm reduction; very brief advice; usual care

INTRODUCTION

The health of people experiencing homelessness is extremely poor compared with the housed population and smoking is a significant contributor to this (1–3). Smoking prevalence rates amongst people experiencing homelessness range between 57% and 82% (4), making it three to four times higher than the national UK average of 14.1% (5). Smoking is a leading cause of death in people aged 45 and over who are homeless, and the second leading cause of death in adults under this age (2). There is an urgent public health need to improve the lives of people experiencing homelessness and reducing the burden of smoking would significantly advance this.

Against a backdrop of research focused on reducing tobacco related health inequalities, there is a growing evidence base on smoking cessation and homelessness (4,6). We conducted a systematic review of studies on smoking prevalence, interventions, and facilitators and barriers to quitting in people who are homeless (4); of 53 studies identified, only two had been conducted in the UK (one of which was by our group (7)). Studies from the US and Australia have explored a range of interventions for smoking cessation amongst people experiencing homelessness including, motivational interviewing, cognitive behavioural therapy, quit lines, nicotine replacement therapy (NRT) and/or other pharmacotherapies (e.g., 8–10). From our review, the reported point prevalence (24 hour or 7 day) abstinence rates at 6 months were modest, ranging between 4% and 13.6%. One small study in the US, showed that for veterans experiencing homelessness much higher 26-week past 7-day point prevalence abstinence rate of 45% (9/20) were reported when using contingency management; participants could earn up to \$815 for carbon monoxide (CO) verified abstinence alongside use of NRT, bupropion and a smartphone app (11). In the only study reporting 6-month sustained abstinence, nobody quit (9). A recent Cochrane review (6), of the 10 intervention studies to reduce smoking, concluded that there was insufficient evidence to assess the effects of any intervention, although there may be modest improvements when offering more intensive interventions. The included studies were deemed to be of low or very low quality; issues with design (e.g., lack of randomisation) as well as substantial imprecision owing to the small number of events and small sample sizes (ranging from n=11 to n=645) resulting in insufficient statistical power in some studies. Follow-up times varied, but 7 of the included 10 studies did assess outcomes at 6 or 12 months (usually point-prevalence) and these were CO validated where possible, however drop out across studies was high. The authors concluded that more high-quality randomised control trials (RCTs) investigating ways to support people experiencing homelessness to quit smoking are urgently needed, these should be sufficiently powered, retain participants for at least 6-months and work to retain participants until these end points.

Feelings of guilt, shame, stigmatisation and undesirable or unhelpful past experiences with treatment services have been reported to contribute to reduced quitting success and an impediment to accessing cessation support (12). There are also studies which highlight the negative views of, and a lack of interest in using, established cessation approaches such as NRT with a preference to engage in self-defined, alternative tobacco harm-reduction (THR) interventions such as e-cigarettes (EC) (7,12). As well as being perceived more positively, EC may also offer a cost benefit for those on a low or no income as EC can be cheaper than smoking. However, the initial start-up cost may be a barrier to use. In our survey of 283 smokers accessing homeless services across Great Britain (GB), we found that, although willingness to use EC was high, only 34% reported that they were willing or able to spend £20 or more on a starter kit (7).

Evidence for the efficacy of EC for smoking cessation is accumulating; in a Cochrane review published in 2021 (13), across 3 RCTs with 1498 smokers, there was moderate certainty that EC were almost 70% more effective than NRT for long-term (defined as 12-months) smoking cessation (RR: 1.69; CI 1.25 – 2.27). Higher quit rates were also found with EC compared with behavioural support across 4 studies (N = 2312; RR: 2.50; CI 1.24-5.04) although the certainty here was low due to imprecision and risk of bias. EC may therefore be a viable alternative to traditional pharmacotherapies for smoking cessation in this population, especially if offered free of charge at homeless centres where relationships with staff are already established.

To explore the feasibility of offering EC to adult smokers accessing homeless services we conducted a cluster feasibility trial (14) in four centres, three were in England and one was in Scotland (14,15). In this trial, two clusters were assigned to offer participants usual care (UC) which consisted of the standard offer of referral to the local stop smoking service (SSS) and two clusters offered participants a free EC starter pack, which consisted of one refillable battery-operated EC device and e-liquid was provided once per week for 4-weeks. The results showed the intervention was acceptable to both staff and participants. We were able to meet our progression criteria as over half of all participants invited were recruited to the study (N=80 in a 5-month period) and we exceeded 50% retention at each and every follow up point. We were also able to collect the majority of the information needed for an economic evaluation and reports of unintended consequences (e.g. adverse effects, trading the device) were very low. The 24-week sustained biochemically validated abstinence [ITT] rates were 6.25% [EC] vs. 0% [UC]).

Building on our feasibility study, here we aim to conduct a two-arm multi-centre cluster randomised controlled trial (cRCT).

Objectives:

Primary: To determine the 24-week sustained, biochemically validated abstinence rates in smokers offered EC compared to UC.

Secondary:

1. Among those who have not achieved full abstinence, to compare the number reporting at least fifty percent smoking reduction at 24 weeks in the EC versus the UC arm.
2. To compare the number achieving 7-day point prevalence quit rates at 4-, 12- and 24-week follow-up in the EC versus the UC arm.
3. To document changes in risky smoking practices (e.g., sharing cigarettes, smoking discarded cigarettes) from baseline to 4-, 12- and 24-weeks in both EC and UC arm.
4. To determine the cost-effectiveness of the intervention
5. To document fidelity of intervention implementation; mechanisms of change; contextual influences and sustainability.

METHODS

Design

A multi-centre cRCT with internal pilot, with 1:1 cluster randomisation to either an offer of an EC starter kit (including e-liquid) (intervention, $n=16$ clusters) or UC comprising very brief advice to quit and signposting to the local SSS (control, $n=16$ clusters).

In-built pilot

To assess the sustainability of the trial, a 6-month internal pilot with the first 120 participants (8 centres) is included to monitor recruitment within the given timeframe. After 6 months, based on individual level recruitment rates from the first 8 centres, the decision to proceed is based on the following progression criteria: Green: 90% recruitment achieved = go. Amber: 60-89% recruitment achieved = present action plan to Trial Steering Committee (TSC) with strategies for overcoming identified recruitment barriers. TSC to manage this plan without involvement of the study funder, and formally assess recruitment again at 12 months. Red: <60% = Rescue plan considered by TSC and funder; joint decision on whether the study should continue.

Setting

The study will take place in 32 homeless day centres across five areas of GB: London ($n=8$), South-East England ($n=6$), East-Anglia ($n=6$), Wales and Southwest ($n=6$) and Scotland ($n=6$). The centres will be

homeless centres, offering a range of support during day-time hours, but do not offer sleeping accommodation or residency as their exclusive provision.

Centres will be recruited into the trial over a 16-month period. Centres within a 100-mile radius of the collaborating Universities have been identified and those which meet the criteria (i.e. day/drop in centre; primarily targeted at the homeless; not already providing EC to service users; within 2 hours travelling distance from each University) are being invited to participate. The first 32 centres that agree to work with us will be recruited.

Participants

People who smoke who are experiencing homelessness in GB, defined here as adults without secure or long-term accommodation and accessing one of the homeless centres in this study.

Inclusion criteria: Participants aged 18+, self-reported daily smoking as verified by staff working at the homeless centres, known to centre staff and willing and able to provide written informed consent. A translator can be provided for those participants who are not able to read English. To represent this population of smokers as accurately as possible, we will not exclude participants based on a physical or mental health diagnoses or other substance-use disorders. Participants must indicate they are willing to try an e-cigarette or any other method of quitting smoking but do not need to be motivated to quit (i.e., willing to engage with the study but make no commitment to quitting).

Exclusion criteria: Pregnant or breastfeeding, a never or former smoker, allergies to any of the e-liquid ingredients, engaged in an active quit attempt, currently using a smoking cessation aid (i.e. at baseline, although the use of another smoking cessation aid is permitted at follow up). While pregnancy is currently an exclusion criterion, this will be reviewed as safety data from ongoing RCTs reporting becomes available up to the point of the first data collection.

16 members of staff in the EC arm, purposively sampled from 8 centres (4 in England, 2 in Scotland and 2 in Wales) will also be recruited for process evaluation interviews.

Recruitment

Recruitment will commence from February 2022 and is planned to continue until June 2023.

Recruitment is managed by centre staff and is restricted to an upper limit of 18 per centre due to cluster size. Participants who meet the inclusion criteria will be identified by staff and asked for

expression of interest before the centre is informed of their allocated condition (EC v UC). The first 15 expressing an interest will be invited to an appointment with the researcher to complete informed consent. If 15 eligible participants have not been identified by this stage, staff in centres will continue to gain expressions of interest.

Staff will discuss the project with potential participants and for those who express an interest, the staff member will make an appointment with the research team for the baseline assessment (including consent).

The research team will introduce themselves, and the study, to service users at each centre. Interviews with participants in our feasibility study (14) revealed high levels of suspicion around research and distrust of external visitors. A candid and open discussion with potential participants should help to alleviate these concerns, build rapport and increase recruitment and retention.

Sample size

Assuming, 0.05 alpha (two-tailed), 90% power, and cluster size of 15 participants (the feasibility study average in day centres (14)), this trial requires 240 participants per arm and 16 clusters per arm (480 participants and 32 clusters in total) to detect a difference of 5.75% between arms (i.e. 6.25% vs 0.5% respectively in the EC vs UC arms) using the power command in Stata 15. The intraclass correlation coefficient (ICC) was set at 0.01 assuming equal cluster sizes. A final sample of 480 provides at least 90% power if the cluster size was smaller ($n = 12$) or greater ($n=18$) than the planned 15 participants per cluster. No adjustment for attrition is applied to the sample size calculations as participants lost to follow-up will be classified as smokers as per Russel Standard.

There is sufficient power to detect more modest differences with smaller cessation rates in the EC arm; for example, with 5% cessation rate in the EC arm (vs. 0.5% UC), allowing 81% power with an ICC of 0.01 and 74% with an ICC of 0.025.

Sensitivity sample size calculations were conducted for the secondary outcome measuring 50% CO reduction, as previous studies have shown that CO reduction is a good predictor of future successful smoking quit attempts (16). If we assumed a minimally clinically important difference (MCID) to be 10% (i.e. 13% EC vs. 3% NRT), for 90% power, ICC = 0.01, alpha = 0.05 (two-tailed) and cluster size 15, we would need 360 participants across 24 clusters in total. If abstinence rates were higher than observed in the pilot (e.g. 1%), the trial would still have 82% power assuming all other assumptions are the same.

Intervention

Delivery of the EC intervention will be as per our feasibility study (14). Centre staff will provide EC arm participants with a tank-style refillable EC starter kit (the PockeX device used in our feasibility study and reconfirmed through recent public and patient involvement (PPI), a choice of nicotine strength e-liquids (12mg/mL & 18mg/mL) and flavours (tobacco, menthol or fruit) and an EC fact-sheet (developed for, and used in, our feasibility study). E-liquids (five 10mL bottles) will be supplied weekly for four weeks by centre staff, five bottles are always provided regardless of levels of use. Participants will be given time to try different flavours and nicotine strengths at baseline and be permitted to switch between flavours in accordance with documented vaping practices (17). EC charging will be available at homeless centres. Although signposting and the provision of local SSS details do not form part of the EC intervention (as above), if participants make enquiries regarding their local SSS (we believe this would be rare) they can be signposted in the usual way as per homeless centre protocol. This information would be recorded as part of the standard health care utilisation questionnaires administered at each follow up point (see economic evaluation section).

Comparator

The control intervention will form Usual Care (UC) defined here as very brief advice (VBA) about smoking cessation (in the form of an 'NHS choices' leaflet adapted for this population, as used in our feasibility study) and signposting to the local SSS with information about their local service. Although some homeless centres do offer more than this, this is not standard practice. Any centres with an established EC 'in house' provision or EC funding stream will be excluded. However, support or provision of EC from local SSS will be permitted as this constitutes part of UC. SSS vary widely in terms of services they offer; although all SSS offer NRT and behavioural support, in 2019, only 11% of local authority funded SSS in England offered EC as part of their service (18), whereas others who consider themselves 'e-cigarette friendly' offer support and advice around EC use. In cases where homeless centres do not have established links with their local SSS (the majority), we will facilitate these links and liaise with the relevant SSS.

Procedure

Figure 1 presents the study flow diagram and data collection at each time point. Table 1 presents the schedule of assessment at baseline and follow up.

- Figure 1: flow diagram here

Table 1: Schedule of enrolment, interventions, and assessments.

TIMEPOINT**	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close-out
	<i>Baseline</i>	0	4-week	12-week	24-week	t_x
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
<i>Usual care</i>		X				
<i>EC</i>		X				
ASSESSMENTS:						
<i>Sociodemographic characteristics</i>	X					
<i>Mental health status</i>	X					
<i>CO breath sample</i>	X		X	X	X	
<i>Smoking behaviour (incl. risky smoking practices)</i>	X		X	X	X	
<i>Motivation to Stop Smoking (MTSS)</i>	X		X	X	X	
<i>Fagerström Test of Cigarette Dependence (FTCD)</i>	X		X	X	X	
<i>7-day point prevalence & 50% smoking reduction</i>			X	X	X	
<i>Thoughts about EC</i>	X		X	X	X	
<i>Adverse effects</i>	X		X	X	X	
<i>Use of EC & unintended consequences (EC arm)</i>			X	X	X	

EC positive effects & EC support (EC arm)			X	X	X	
Smoking cessation support received	X		X	X	X	
Health-care service use	X		X	X	X	
Health Related Quality of Life	X		X	X	X	
Substance use	X					
AUDIT-C	X					
Assessment of main effectiveness outcome					X	
Debrief					X	X

Eligibility assessment

Participants will be screened for eligibility by the centre staff, they must be both known to the centre staff and a known current smoker. Details of other inclusion criteria are presented above.

Consenting

At the baseline appointment participant consent will be obtained by the researcher to: a) take part in the study, b) be contacted regarding participation in qualitative process evaluation interviews, c) the sharing and appropriate linkage of anonymised data in accordance with the London South Bank University and European Social Research Council research ethics and government policies, and d) long term (up to 2 years) follow up (beyond the outcomes to be collected in the funded study). Individuals (participants and staff) agreeing to take part in the qualitative process evaluation interviews will provide further written consent prior to interviews and will consent to a) recording the interviews and b) the use of anonymised quotes in reports and publications.

Baseline assessment

Table 1 presents the schedule of assessments. At baseline, participants will be asked to complete both the consent form and the baseline assessment measures (see measures, below). If participants cannot

complete both on the same day, consent will be taken and another appointment to complete the baseline assessment will be arranged.

Randomisation

Participating centres will be randomly allocated to the EC intervention (n=16) or Usual Care (n=16). The intervention the participant receives will be based on their centre's allocation. The trial statistician will create the randomisation list, which will be embedded/read in REDCap, which will be hosted by Kings College London (KCL).

Intervention and comparator delivery

As per our feasibility study protocol, the intervention will be delivered by centre staff (Figure 1). The researchers will be involved in the data collection only. Training for staff will commence before recruitment (within two weeks. Staff training will focus on a) delivery of the study and, b) smoking cessation and tobacco harm reduction. Training will be to the standard by National Centre for Smoking Cessation and Training (NCSCT) recommendations (19): Information on smoking prevalence and patterns in the general population and in disadvantaged groups; health effects of smoking and benefits of cessation; evidence based smoking cessation treatment; misperceptions around smoking cessation in the context of other addictions and mental illness and study importance. Additionally, staff in the EC arm will be provided with information on the evidence base of EC use and effectiveness and information about how to deliver correct advice about EC to participants, along with a practical hands-on demonstration and practice of EC (full details can be found at (14)).

Recruitment will begin within two weeks of staff training. The researcher is responsible for gaining consent and will conduct the baseline assessment and centre staff will then deliver the intervention – either an EC or UC as per cluster assignment above (see above 'Intervention and comparator delivery')

Follow-up data collection

Follow-up participant data will be collected, in-person by the research team, at weeks 4, 12 and 24 after baseline assessment. Qualitative interviews (to address secondary outcome 5) will be conducted by the research team in four centres in the EC arm, with staff (N=16) between weeks 4-8, and with service users/participants (N=32) between weeks 12-24. Researcher observations around week 4 will also capture information on fidelity of intervention implementation and contextual influences.

Staff are responsible for offering the 4-weeks provision of e-liquid and they are required to monitor uptake of the liquids and report this to the research team.

Debriefing

All participants who attend the 24-week follow up appointment or withdraw from study will be debriefed (where possible). At this point, participants will be given further information about the trial including overall aims and expected outputs, this will be accompanied by information on the NHS SSS.

MEASURES

Table 1 presents the following assessments at the point of use throughout the trial.

Sociodemographic and housing characteristics: Sex, age, ethnicity, education, employment and immigration status, access to government benefits (recourse to public funds) and current housing status including where the participant stayed the night before the assessment will be recorded.

Mental health status: This will be recorded by asking if the person has a diagnosed mental health condition.

CO breath sample: Participants will be asked to hold their breath for 15 seconds and then to blow out slowly into a disposable mouthpiece attached to a Bedfont Pico Smokerlyzer. Sample taken by research assistants.

Smoking characteristics and behaviour: Cigarettes smoked per day, smoking history (e.g., length of time smoking, previous quit attempts), severity of tobacco dependence as measured by the Fagerstrom Test of Cigarette Dependence (FTCD (20), the Motivation to Stop Smoking Scale (21), risky smoking practices (e.g., sharing cigarettes with others “going-twos” and smoking discarded cigarettes) and CO breath sample will be recorded.

Thoughts about EC: Two questions examining the extent to which participants agree or disagree with the statements “e-cigarettes can help people stop smoking” and “e-cigarettes can help people reduce their smoking”. (1 Strongly agree – 5 Strongly disagree). Perceptions of harm of e-cigarettes compared with cigarettes (as measured elsewhere (22)).

Use of the EC, effects of use, unintended consequences, support of use (EC arm only): Questions relating to possession of the EC or whether the device has been lost, stolen, sold, exchanged, swapped or given away or broken, use of the device, reasons if stopped using it, if any additional non-e-liquid substance

have been added to the device. Effects from the EC, including how satisfying and pleasant the EC is how it tastes and how helpful it was in reducing craving, and three questions relating to staff and social support around use of the device are included.

Adverse effects: Participants will be asked to indicate on a 5-point Likert scale (1 not at all – 5 extremely) if they have felt any adverse health effects over the previous week, these include the most commonly reported adverse effects in previous trials (13) and those from the pre-trial feasibility study (14) e.g. cough, shortness of breath, dizziness, weak and nauseous (full list not included).

Smoking cessation support received: Receipt of support for smoking cessation including advice or medication/products from a health practitioner and receipt, self-purchase, and use of licensed nicotine replacement therapies.

Use of health care services: Travel time and costs to health appointments, and Health Related Quality of Life as measured by the EQ-5D-3L will be recorded.

Substance use: To measure alcohol use the AUDIT-C a brief 3-item questionnaire (23) is included, and for other substances a single question asking if in the last month any illicit substances have been used.

Primary outcome measures

Sustained CO validated smoking cessation at 24-weeks using the Russell Standard for cessation trials (i.e. no more than 5 cigarettes since 2 weeks post target quit date [TQD] validated by expired CO <8ppm (24) and intention to treat analysis i.e. analysis will be according to treatment allocation (regardless of compliance or crossover), all participants will be included in the primary analysis, and those lost to follow up, who fail CO validation or refuse to provide a CO reading, will be treated as non-abstainers.

Secondary outcomes measures

Fifty percent smoking reduction (calculated by reduction in self-reported cigarettes per day (CPD) from baseline) at 24 weeks; 7-day point prevalence quit rates at 4-, 12- and 24-weeks; self-reported changes in risky smoking practices (e.g. sharing cigarettes, smoking discarded cigarettes) from baseline to 4-, 12- and 24-weeks; cost-effectiveness of the intervention; fidelity of intervention implementation; mechanisms of change; contextual influences and sustainability.

Data management and monitoring

The data will be managed via the REDCap password protected system. The research team will enter the data which will be checked by areas leads and overseen by the clinical trial manager.

Analysis

Participants' demographic and smoking characteristics at baseline will be presented broken down by trial arms. We will present means and standard deviations for continuous measures that are approximately symmetric; median and quartiles if the distribution is skewed. Discrete outcomes will be described using both the number and proportion (percentage). Similarly, we will present summary measures of the primary and secondary outcomes.

The primary analysis will use mixed-effect model with random effects for clusters and fixed effect for treatment to compare the two arms on quit rates. Logistic mixed-effect model will be used for binary outcomes. The model will be adjusted for cluster-level. Sensitivity analyses of the primary outcome will be adjusted for individual-level variables that differ between arms at baseline (25). The results of the main analysis of the primary outcome will be presented as a difference in proportions (95%CI) and the number needed to treat (95%CI) will also be estimated based on the results of the primary endpoint.

The pattern of missing data by baseline characteristics will be explored. Sensitivity analyses will be conducted to assess the robustness of conclusions to missing outcome data (complete case analysis, multiple imputation) and departures from randomised treatment (per protocol analysis).

A detailed statistical analysis plan will be developed by the trial statistician and reviewed by the independent statistician. It will be finalised prior to completion of data collection and agreed with the TSC.

Economic evaluation

This will be an incremental cost-effectiveness of the EC intervention over and above the UC intervention.

The costs of providing the EC intervention will be recorded including the costs of training, staff time and overheads and the EC products. We will collect costs prospectively and apply local unit costs to the quantities of each resource utilised. We will also record the costs of providing UC.

Following NICE guidance (26), we will collect health care utilisation data for contacts with the NHS and personal and social services (PSS) using a bespoke service use questionnaire. This includes the use of primary and secondary health care services and social care. Quantities recorded are multiplied by national average unit costs (27,28) to derive a cost profile for each patient. The service use questionnaire includes patients' out of pocket expenditure on cessation aids, costs of travel to health services and lost productivity.

EQ-5D-5L (29) will be administered at baseline and each follow up. The UK social tariff is applied to derive Quality Adjusted Life Years (QALYs). We will use the tariff recommended by NICE at the time of analysis to calculate QALYs as the primary outcome for the economic evaluation (28,30). We will present a secondary analysis using the cost per quitter from an NHS/PSS perspective and a societal perspective (including patient cost of buying cessation aids, travel and productivity).

We will calculate QALYs using the QALY profiles as plotted at baseline and each follow-up point using the standard area under the curve method (30). Patient costs are combined with QALYs to estimate the incremental cost per QALY. The health economic analysis will use an existing model to extrapolate the longer-term cost-effectiveness (31). Uncertainty around the decision to adopt the intervention is assessed using non-parametric bootstrap re-sampling. Bootstrapping is an efficient method for calculating the confidence limits for the incremental cost-effectiveness ratio (ICER) as its validity does not depend on any specific form of underlying distribution. The process for the bootstrapping uses 5000 replications of sampling with replacement to create a distribution for the ICER. The 95% confidence intervals for the ICERs based on the bootstrapping results are derived from using the 2.5th and 97.5th percentiles. Cost-effectiveness acceptability curves (CEAC) will be constructed based on the bootstrap iterations as outlined above (32) to estimate the probability that the intervention is cost-effective at different threshold values for one QALY.

In addition to addressing the uncertainty surrounding the point estimate of the ICER, sensitivity analysis is undertaken to account for missing data.

Process evaluation

The process evaluation will use both quantitative and qualitative approaches to explore treatment context, fidelity of implementation, mechanisms of change (mediators as per logic model; Figure 2) and sustainability. Methods include observation, checklists, staff evaluation forms, questions within participant baseline and follow-up questionnaires, in-depth qualitative interviews and decision maker

workshops. Further details including methods and data analysis are available in the supplementary file.

- Figure 2 here

Ethical approval

Ethical approval has been gained from London South Bank University (Ref: ETH2021-0176).

Dissemination policy

The results from the project will be published open access and made available to the centres taking part. We will run a series of free to access impact events, which will be informed by our TSC with public involvement. We will adhere to our funders (NIHR) guidelines for publishing. The anonymised data will be made available on the LSBU (study sponsor) open research repository.

DISCUSSION

This trial will be the first cRCT of e-cigarettes offered to smokers accessing homeless services in GB. The results will have significance for researchers, policy makers and clinicians interested how to treat tobacco dependence amongst this population. If shown to be effective and cost-effective, EC may be a viable alternative to smoking for this population and help to reduce the enormous burden of tobacco related death and disease prevalent within this group. Along with the main results, the embedded process evaluation will provide information on mechanisms of change, as well as implementation and scalability.

There are several challenges to this trial, which centre around recruitment and retention. The in-built pilot will assess early recruitment targets with clear targets and protocol for different outcomes. Given the transitory nature of this group and competing health and social needs we will need to work sensitively and flexibly. In relation to retention, we observed retention rates of 75%, 63% and 59% respectively at 4, 12 and 24 weeks in our feasibility study. These rates are similar to those of other studies in this population (4) but could be improved. Interviews with participants in our feasibility study revealed that mistrust, suspiciousness and anxiety around research were key barriers to retention although some participants could not be followed up because they were no longer attending the homeless centre (e.g. due to imprisonment, hospitalisation or had moved out of the area). Since retention (as well as recruitment) is key to the success of the trial, we have conducted two focus groups with eight members of staff and service users at homeless centres about ways to maximise

retention. Psychological intrusion from questionnaires (personal, seemingly irrelevant questions), length of follow up sessions, and appointments with different researchers were raised as additional barriers. We have reduced the length of our questionnaire and removed sensitive questions. We will also attempt, as far as possible, to ensure that the same researcher collects baseline and follow up data with each participant. Other suggestions from our PPI group were to maintain more regular contact with participants between sessions. We will therefore send regular text messages and make telephone calls between appointments (participants were generally quite willing to provide mobile phone numbers). We will also explore the option of following up participants at another mutually convenient location if they are no longer attending homeless centre services.

Another challenge is around the use of an EC; the highly publicised media stories of EC harms have negatively impacted smokers' perceptions of EC; indeed, in our feasibility study qualitative interviews highlighted participant uncertainty around EC. Our training with staff who will be delivering the EC intervention will be updated with the most recent safety and efficacy literature and we will continue to respond to all staff queries if these media headlines are released.

This is an important study but there are some limitations. Firstly, this study is conducted in Great Britain where the homeless population may vary from elsewhere, both in access to health care and specifically smoking cessation support (which is free to access in the UK), the nature of the homeless sector may also differ. Our findings may therefore have little transferability to low-middle-income countries or countries without free, at the point of access health care. E-cigarettes are also a recommended smoking cessation aid in the UK, endorsed by leading public health bodies, minimising the validity of the findings to other countries with more punitive regulations or stricter access.

Conclusion

To conclude, this will be the first cRCT in GB of e-cigarettes versus usual care for people accessing homeless services who smoke, the findings are vital for understanding the impact of ECs in harder to reach, and treat, smokers and also for contributing to the evidence base on what works for smokers experiencing homelessness.

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