Study Protocol

Effects of e-cigarettes vs usual care for smoking cessation when offered at homeless centres: A cluster randomised controlled trial

Short title/Acronym:	Smoking CEssation Trial in Centres for the Homeless/SCeTCH
Sponsor:	London South Bank University (LSBU)
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Version Number:	1.2
Date:	22.02.22
Clinical Trials Registration Number:	18566874
REC reference:	ETH2021-0176
Site(s)	32 homeless centres in Great Britain (GB)
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Funder:	NIHR PHR

Principal Investigator Agreement Page

The clinical study as detailed within this research protocol (Version 1.0), or any subsequent amendments will be conducted in accordance with the
Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

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Principal Investigator Site: London South Bank University & University College London

Signature and Date: 24/9/2021

STUDY SUMMARY/SYNOPSIS

TITLE	Effects of e-cigarettes vs usual care for smoking cessation when offered at homeless centres: A cluster randomised controlled trial
SHORT TITLE	Smoking CEssation Trial in Centres for the Homeless/SCeTCH
Protocol Version Number and Date	1.1 20.01.22
Methodology	Cluster randomised controlled trial (cRCT)
Study Duration	36 months
Study Centre(s)	32 homeless centres across Great Britain
Objectives	***Primary:*** To determine the 6-month sustained, biochemically validated abstinence rates in smokers using EC compared to smokers offered 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.
Number of Subjects/Patients	480 randomised participants
Main Inclusion/Exclusion Criteria	***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. ***Exclusion criteria:*** Pregnant or breastfeeding, a never or former smoker, currently using a smoking cessation aid, unable or unwilling to provide consent, not known to the centre staff, allergic to any of the e-liquid ingredients (EC arm only).

Statistical Methodology and Analysis	Sustained CO validated smoking cessation at 24-weeks using the Russell Standard for cessation trials and intention to treat analysis (i.e. no more than 5 cigarettes since 2 weeks post target quit date [TQD] validated by expired CO <8ppm.Participants lost to follow-up are treated as non-abstainers. Abstinence rates and rates of those sustaining a 50% or greater reduction in baseline cigarette consumption and CO levels will be compared between the study arms. Reductions in the frequency risky smoking practices will be compared between study arms. Frequency of adverse reactions will be compared between arms.

GLOSSARY

AE	Adverse Event
AL	Area Leads
AR	Adverse Reaction
CCA	Complete Case Analysis
CEAC	Cost-Effectiveness Acceptability Curves
CI	Co-Investigator
CO	Carbon Monoxide
CPD	Cigarettes Per Day
cRCT	Cluster Randomised Controlled Trial
CRF	Case Record Forms
CRN	Clinical Research Network
DMC	Data Monitoring Committee
EC	Electronic Cigarette
EOI	Expression of Interest
EQ5D	European Quality of Life -5 Dimensions
FTCD	Fagerstrom Test of Cigarette Dependence
GCP	Good Clinical Practice
HSR	Health, Safety and Resilience
ICC	Intraclass Correlation Coefficient
ICER	Incremental Cost-Effectiveness Ratio
ITT	Intention To Treat
KCL	King's College London
LSBU	London South Bank University
MCID	Minimally Clinical Important Difference
MHRA	Medicines and Healthcare products Regulatory Agency
MTSS	Motivation to Stop Smoking Scale
NCSCT	National Centre for Smoking Cessation and Training
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NRT	Nicotine Replacement Therapy
PHE	Public Health England
PI	Principal Investigator
PPI	Patient and Public Involvement
PSS	Personal and Social Services
QA	Quality Assurance
QALYs	Quality Adjusted Life Years
QC	Quality Control
RA	Research Assistant
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RR	Risk Ratio
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SSS	Stop Smoking Service
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEC	Trial of Electronic Cigarettes
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group
TQD	Target Quit Date
TSC	Trial Steering Committee

UC	Usual Care
VBA	Very Brief Advice

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1 Introduction

1.1 Background

Electronic cigarettes (EC) are electronic vaping devices that are handheld and produce for inhalation, an aerosol formed by heating an e-liquid using a battery-powered heating coil (1).

EC are the most popular quit method used by smokers in the UK (2), and there is growing evidence for their effectiveness in clinical trials (3). EC may be a useful method of quitting for people who are heavily nicotine dependent as they are effective in delivering nicotine over and above other nicotine products. To date, there is less evidence on how effective EC are for smoking cessation for people with pre-existing severe health and social needs. This evidence is needed to fully evaluate their public health and population impact (4).

This study explores the effectiveness of EC versus usual care (UC) in people accessing homeless support services. At the current time, in these settings, UC involves a referral to a traditional NHS stop smoking service (SSS). SSS provide licensed Nicotine Replacement Therapies (NRT) alongside behavioural support. While these methods are effective for many, for others, including those with competing needs, this may not be enough. EC with effective nicotine delivery and ability to replicate some of the sensory aspects of smoking (e.g., hand to mouth action, deep inhalation) may enhance quit rates. Offering EC at a place which people who are experiencing homelessness are already seeking support, may also be advantageous (5).

1.2 Feasibility Data

To explore the feasibility of offering EC to adult smokers accessing homeless services, we conducted a cluster feasibility trial in four centres; three were in England and one was in Scotland (5,6). In this trial, two clusters were assigned to offer participants usual care (UC) which consisted of the standard offer of referral to the local SSS and two clusters offered participants a free EC starter pack, which consisted of one refillable battery-operated EC device and e-liquid 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 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]).

Effects of EC on smoking

Evidence for the efficacy of EC for smoking cessation is accumulating; in the most recent living Cochrane review published in 2021 (3), across 3 RCTs with 1498 smokers, there was moderate certainty that EC were almost twice as effective as 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: 2.5; 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 for adults experiencing homelessness, especially if offered free of charge at homeless centres where relationships with staff are already established.

EC safety

The most recent Public Health England (PHE) evidence review of the literature (7) presents MHRA yellow card notifications of injuries associated with EC use. To date, these are minimal but there are 3 known fatalities, which may be associated with, but not causally related to, EC use.

In the most recent Cochrane review (3), there was imprecision in the findings on safety as measured by reports of AE and SAEs (the confidence intervals were wide). However, comparison analysis revealed no difference in AEs between nicotine and non-nicotine EC use. Incidents associated with SAE and EC use were low. While there is no clear evidence on the harms associated with nicotine EC use, the report concludes that there remains only a small number of studies by which to analyse and within those, follow-up times are less than desirable to measure health and safety outcomes.

In our feasibility study, 21 possible AE were rated, each on a scale of 0 (not at all) to 100 (extreme). The most commonly reported effects were nervousness, headache, sweating, weakness and nausea, each with a mean score below 20. Nausea and headache along with cough and throat/mouth irritation were also the most commonly reported AE in the Cochrane EC review.

Other areas of safety concern have focused on e-liquid content and vapour emissions. While not risk free, it is now well-evidenced that EC are far less hazardous to the user and bystanders than cigarette smoke, with substantially less toxicants and carcinogens detected in exclusive users (4,7,8). A recently published analysis of 40,785 e-liquid containing products ingredient and emission data to the MHRA from November 2016 to October 2017 (9), highlighted some areas for improvement and concern, notably the large range of ingredients and emissions. The MHRA reporting system is unstandardized in terms of reporting requirements, and for quantified emissions, median levels are for the most part below published safe limits for ambient air. However, the authors conclude that, notwithstanding these suggested improvements, EC remain safer than combustible tobacco smoking. As flavours appeal to smokers switching to EC, a balanced approach to reducing absolute risk while not making the products unappealing is required.

1.3 Rationale and Risks/Benefits

People experiencing homelessness have some of the worse health outcomes of all minority and disadvantaged groups, whereas the health inequalities between those in the most advantaged social grades can be described as a slope, the relative disparity between those housed and not housed is more akin to a cliff (10). Smoking is incredibly common amongst this population, up to four times the average UK smoking prevalence rate (11,12). Smoking significantly contributes to excessive morbidity and mortality (10,13,14). At the same time, there is a paucity of evidence of tobacco dependence treatment for this group (11,15). There is strong evidence to suggest tailored interventions, designed to provide support at a place which is already familiar to the person, with established relationships and taking a harm reduction approach, may help people to quit smoking (5,6,11,15,16).

More broadly, as the evidence on EC continues to grow, whether EC can support people facing severe health and social comorbidities is lacking. That is, while EC may assist people to remain smoke free without such competing needs, their effectiveness for more disadvantaged groups requires greater attention. Indeed, turning attention to groups facing disadvantage, was a recommendation in the recent Cochrane review (3). If EC are effective for such groups, they can reduce the burden of smoking related disease within poorer communities and would signal a population wide net positive public health benefit.

Our feasibility study tested whether the offer of an EC was acceptable and whether a full trial would be possible. Early results were promising, and this trial now builds on this work. The aim of this trial is to conduct a two-arm multi-centre cluster randomised controlled trial (cRCT). The following research questions will be answered.

1. What is the effectiveness and cost-effectiveness of providing free EC starter kits to smokers accessing homeless centres compared with UC?
2. How is the EC intervention implemented and how does organisational and geographic context influence implementation?
3. What are the mechanisms through which the delivered intervention activities and participant interactions produce change in smoking behaviour?
4. If the intervention is effective and cost-effective, what are the facilitators and barriers to successful implementation across Great Britain?

2 Trial Objectives and Design

2.1 Trial Objectives

Primary Objective - To determine the 6-month sustained, biochemically validated abstinence rates in smokers using EC compared to smokers offered UC.

Secondary Objectives -

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.

2.2 Trial Design

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

A 6-month internal pilot with the first 120 participants (8 centres) is included to monitor recruitment within the given timeframe. The following stop/go criteria are specified: 90% recruitment achieved = go. Amber: 60-90% recruitment achieved = present action plan to Trial Steering Committee (TSC) with strategies for overcoming identified recruitment barriers. TSC to manage this plan with 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.

2.3 Setting

The study will take place in 32 non-residential homeless centres across five areas of GB: Scotland (N=6), Wales (N=3)Southwest (N=3), East England (N=6), Southeast England (N=6) and London

(N=8). Centres will be eligible if they are not exclusively residential; primarily targeted at people experiencing homelessness; not already providing EC to clients; and within 2 hours travelling distance from area university. Centres will need to agree to be randomised to either arm.

3 Subject Selection

3.1 Number of Subjects and Subject Selection

480 participants will be recruited from 32 homeless centres across Great Britain (15 participants per centre). Participants will be told about the study by centre keyworkers and, if interested, an appointment will be made to see a researcher to sign up for the study. Participants must be known smokers and known to the centre.

3.2 Inclusion Criteria

- Participants aged 18+
- Self-reported daily smoking as verified by staff working at the homeless centres
- Known to the homeless centre staff
- Willing and able to provide written consent (a translator can be provided)

3.3 Exclusion Criteria

- Pregnant or breastfeeding (to be reviewed upon new evidence)
- Never or former-smoker
- Currently using a smoking cessation aid
- Unable or unwilling to provide written consent
- Allergic to any of the e-liquid ingredients (EC arm only)
- Not known to the centre staff

allergic to any of the e-liquid ingredients (EC arm only)
4 Study Procedures

4.1 Informed Consent Procedures

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) . Individuals (participants and staff) who have indicated they are happy to be contacted to take part in an interview (process evaluation) will be followed up by local area RAs to confirm their participation. Those agreeing 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.

4.2 Screening Procedures

Potential participants will be screened for eligibility by keyworkers before being invited to take part and further screening checks will take place during the baseline session.

4.3 Randomisation Procedures

Centres will be randomised (1:1 in permuted blocks), allocated to the EC intervention (n=16) or Usual Care (n=16) using permuted block randomisation to ensure balance. Where possible, staff at centres will obtain expressions of interest (EOI) from potential participants who meet the inclusion criteria *before* the centres receive training and are made aware of their allocated condition. Researchers will approach the first 15 who have expressed an interest in the study and invite them to a baseline session where informed consent will be taken. This approach is preferred over randomly selecting participants from the EOI list to reduce disharmony among clients attending centres. Our final sample size allows us to retain 90% if we under or over-recruit by +/- 3 in each centre (see section 6.3). 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).

4.4 Schedule of Treatment for each visit

Figure 1 presents the flow diagram of the schedule of treatment for each arm. Table 1 presents the assessments within each arm.

Staff training

Staff training needs have been identified from our scoping and PPI work and we have developed and tested a 2-hour education and training course in our feasibility study. Training will be provided for staff at each centre in both arms immediately prior to the recruitment period. The educational content follows National Centre for Smoking Cessation and Training (NCSCT) recommendations. This includes: 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. Information about how to deliver correct advice about EC to participants will be provided along with a practical hands-on demonstration and practice around EC assembly, how to use the device, charge it, refill the tank, replace coils and battery safety is also provided. Staff in the UC arm will receive additional information about how to signpost clients to their local SSS.

Control Group

The control intervention will form usual care. Usual care (UC) here is defined as very brief advice (VBA) about smoking cessation 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. In line with the current level of provision for smoking cessation in homeless centres, our control arm will include VBA to quit (in the form of an 'NHS choices' leaflet adapted for this population as used in our feasibility study) and signposting to the local SSS, including information about the location and opening hours of the service. Any centres with an established EC 'in house' provision or EC funding stream will be excluded (although this is uncommon). 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, only 11% of local authority funded SSS in England offer EC, whereas others who consider themselves 'e-cigarette friendly' offer support and advice around EC use.

Intervention Group

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 (e.g., the PockeX as used in our feasibility study, a choice of nicotine strength e-liquids (12mg/mL & 18mg/mL) and flavours (tobacco, menthol or fruit) and an EC factsheet (developed for, and used in, our feasibility study). E-liquids (five 10mL bottles per week) will be supplied for four weeks at weekly intervals by centre staff. 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 (21). EC charging will be available at homeless centres. Participants receiving this intervention will not be discouraged from accessing their local SSS. 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).

4.5 Measures

- Demographic details, smoking history and housing status
- Fagerstrom Test of Cigarette Dependence (FTCD) (17)
- Motivation to Stop Smoking Scale (MTSS; (18))
- Adverse reactions – 13 adverse reactions (nervous, headache, sweaty, weak, nausea, pounding heart, throat/mouth irritation, sleep disturbance, dizziness, shortness of breath, cough, wheezy, phlegm production) based on those reported in our feasibility study (5), the Cochrane review of EC (3) and the English TEC study (19), each rated on a 5-point scale from 1 (not at all) to 5 (extremely)
- Positive effects - 5 positive effects (hit, pleasant, satisfying, tastes good, helpful for reducing urge to smoke) based on those most commonly reported in our feasibility study (5)
- Risky smoking practices (sharing cigarettes, pickup up discarded cigarettes, asking strangers for cigarettes) each rated on a 4-point scale (not at all, occasionally, regularly, daily)
- Thoughts about EC (perceptions of harm, usefulness for quitting, acceptability)
- EC support (i.e. from staff at centres and others)
- Unintended consequences (of supplying free EC starter kits) including theft, loss, exchanges, breakages, adding other substances.
- Self-reported smoking status
- End-expired carbon monoxide reading: Collected using a calibrated CO monitor. A reading of <8ppm will be used as a cut-off for abstinence
- Use of EC/NRT (including use in the UC arm). Participants who stop using EC/NRT will also be asked their reasons for doing so.
- European Quality of Life-5 Dimensions (EQ5D) questionnaire at baseline and each follow up point.
- Smoking cessation service and health service use at baseline and each follow up point.
- Use of personal and social services
- AUDIT-C
- Diagnoses of mental illness: binary yes/no response

4.6 Outcomes

4.6.1 Primary Outcome

Sustained CO validated smoking cessation at 24 weeks using the Russell Standard for cessation trials and intention to treat analysis (i.e., no more than 5 cigarettes since 2 weeks post target quit date [TQD] validated by expired CO <8ppm. Participants lost to follow-up are treated as non-abstainers).

4.6.2 Secondary Outcomes

Fifty percent smoking reduction from baseline to 24 weeks; 7-day point prevalence quit rates at 4, 12 and 24 weeks; changes in the frequencies of 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

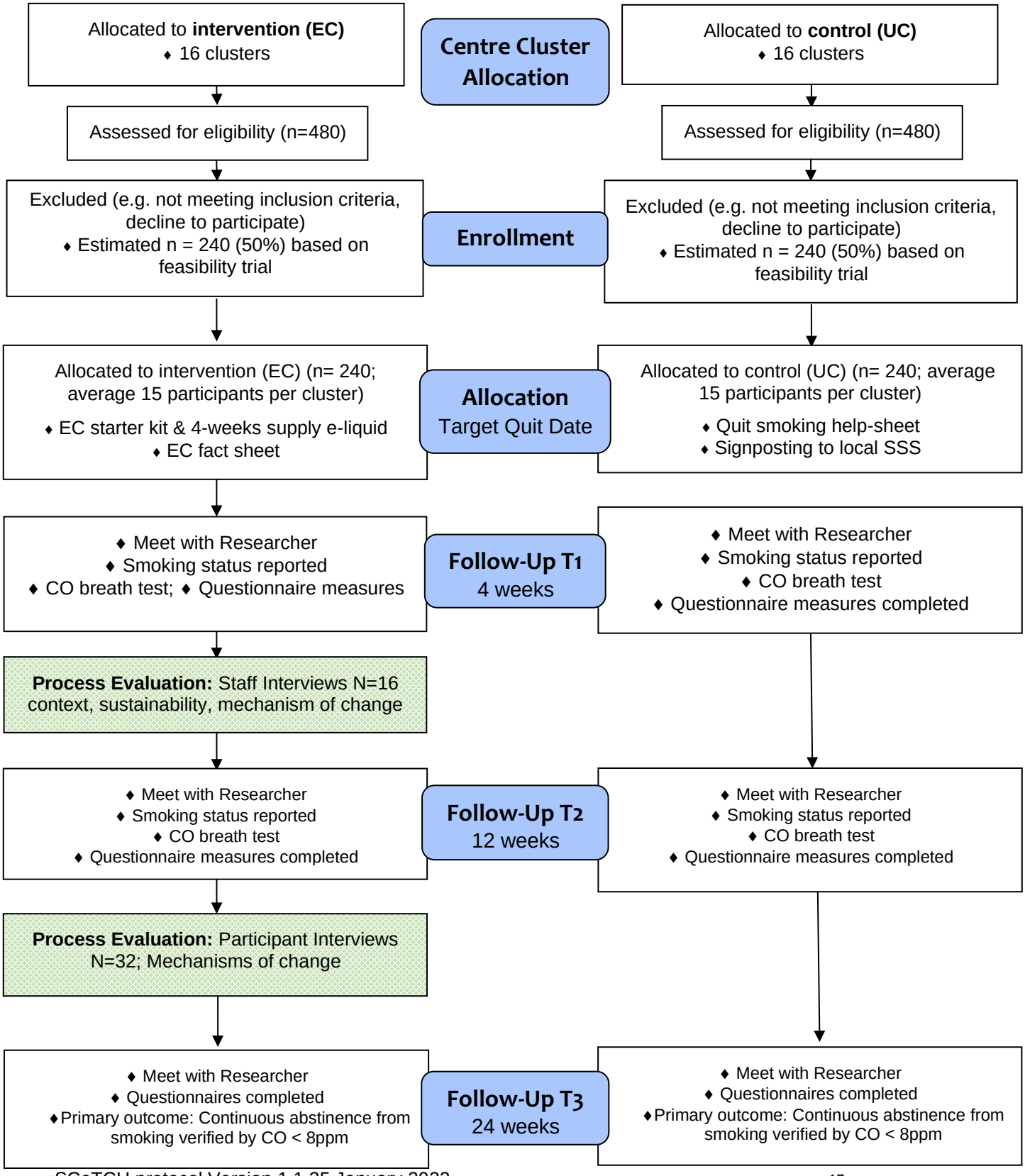
4.7 Study product

As per our feasibility study we will continue to use the Aspire PockeX, a second-generation refillable tank device, the device comes with a charger. We also supply e-liquid once per week for the first 4-weeks, participants have a choice of flavours (2 tobacco, 1 menthol, 1 fruit), and rubber bands designed to reduce tank breakages. We will monitor problems and events associated with product use.

4.8 Flow Chart of Study Procedures

Figure 1: Flow Diagram

Effects of E-cigarettes (EC) versus Usual Care (UC) for smoking cessation when offered at homeless centres: a cluster Randomised Controlled Trial (cRCT)



4.9 Schedule of Assessment

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

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

4.10 End of Study Definition

The study would be completed, and the REC informed after the final attempt to collect 6- month follow-up data from the last randomised participant.

4.11 Subject Withdrawal

Participants will be able to withdraw from the study up until the time the results are written up. This will not affect their use of the homeless centre or impact other treatments. Unless withdrawn participants request otherwise, data collected up to the point of their withdrawal will be used in the study analysis. Participants will be withdrawn if they withdraw their consent to participate. We do not foresee any other reasons to withdraw participants.

4.12 Data Collection and Follow up for Withdrawn Subjects

Participants who have requested withdrawal will not be followed up at subsequent follow up points unless they wish to be.

5 Adverse event/reaction reporting

5.1 General Definitions

5.1.1 Adverse Event (AE) and Adverse Reaction (AR)

An AE is any untoward medical occurrence in a participant who has undergone any research procedure including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of the study product.

An AR is an AE that may have a causal relationship with the research procedure that the participant has undergone. All AEs judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to the study treatment qualify as an AR.

5.1.2 Serious Adverse Event (SAE) and Serious Adverse Reaction (SAR)

A SAE/SAR fulfils at least one of the following criteria:

- Is fatal – results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Deemed by the PI to be medically significant

5.2 Investigators Assessment

5.2.1 Seriousness

Adverse events/reactions will be assessed for seriousness by the PI or a medically qualified delegated team member according to the definitions given in section 5.1.2.

5.2.2 Relatedness

The PI or delegate will assess whether there is a reasonable possibility that the AE is related to a trial treatment or procedure.

5.2.3 Expectedness

The following ARs are deemed potentially related to the study treatment: nausea, throat/mouth irritation, cough, headache, sweaty, weak and sleep disturbance and these will be rated at each follow up point. The PI or delegate will use this list to determine whether the AE is an expected reaction to the trial treatment or procedure.

5.2.4 Severity

Expected AR will be rated by study participants at each follow up point. For any receiving a score of 5 (extremely), participants will be asked whether this has stopped them for doing things that they would normally do as an indication of severity. The severity of the event/reaction will be assessed by the PI or delegate according to the following terms and assessments. The intensity of an event should not be confused with the term “serious” which is a regulatory definition based on patient/event outcome criteria.

Mild: Some discomfort noted but without disruption of daily life
Moderate: Discomfort enough to affect/reduce normal activity
Severe: Complete inability to perform daily activities and lead a normal life

5.3 Notification and reporting Adverse Events or Reactions

Data on AEs, ARs, SAEs and SARs and will be collected and recorded on the CRF/REDCap including i) whether an AE has occurred; ii) what they event was; iii) whether the AE was deemed serious (i.e. a SAE); iv) whether the AE was deemed related to the trial treatment/procedure (i.e. an AR); v) whether the AR was expected; and vi) severity of the AR. If the AR is **not** defined as SERIOUS, the AR will be recorded in the CRF and the participant will be followed up by the research team.

5.4 Notification and Reporting of Serious Adverse Events/Reactions

All SAEs including SARs will be recorded in the participant’s notes and CRF. This should include a description of the event, the date and time that the event began and ended (or ongoing), the severity of the event and any action taken in response to the event. SAEs and SARs should be reported immediately to the PI and/or TM. The PI or TM must report **related and unexpected SAEs to the REC/sponsor** via the relevant project page on Haplo (Research and Enterprise Management) within 24 hours of the PI, TM or co-investigators becoming aware of the event. Nominated co-investigators can be authorised to complete SAE forms on Haplo in the absence of the PI/TM at the co-ordinating site. The original hard copy and any subsequent follow up of SAE forms must be kept with the participant CRF under double-lock conditions at the study site until the end of the trial.

SAEs and SARs will also be reported to the DMC and to the funder (NIHR) via uploading DMC minutes and through progress report tasks.

6 Statistical Considerations

6.1 Primary Endpoint

CO validated sustained abstinence rates at 24-weeks post baseline assessment/enrolment.

6.2 Secondary Endpoints

- CO validated sustained abstinence rates at 4, 12 and 24 weeks post
- 7-day point prevalence abstinence at 4, 12 and 24 weeks
- 50% Smoking reduction in participants who did not achieve full abstinence at 24 weeks
- Changes in the frequencies of risky smoking practices from baseline to 4, 12 and 24 weeks
- Adverse reactions
- Cost-effectiveness of the interventions over the 24 week trial period.

Abstinence at 4 weeks after TQD would be defined as a self-report of no smoking of conventional cigarettes (not a puff) for the previous 2 weeks, validated by a CO reading of <8ppm. Participants who do not provide a CO reading at Week 4 will be considered to be smoking. 12 and 24 week sustained abstinence will be calculated in accordance with the Russell Standard [50] as a self-report of smoking no more than 5 cigarettes since 2 weeks post-TQD validated by CO readings < 8ppm. Participants lost to follow-up or not providing biochemical validation will be included as non-abstainers.

6.3 Sample Size

Our sample size is based on our feasibility trial. For, 0.05 alpha (two-tailed), 90% power, and cluster size of 15 participants (the feasibility study average in day centres (5)), 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). The intraclass correlation coefficient (ICC) was set at 0.01 assuming equal cluster sizes. A final sample of 480 provides 90% power if the cluster size was smaller (n = 12) or greater (n=18) than the planned 15 participants per cluster.

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 (20). If we assumed a minimally clinical 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.

6.4 Statistical Analysis

Analyses will be undertaken after the last participant has completed the 6-month follow-up.

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. The model will be adjusted for cluster-level and individual-level variables that differ between arms at baseline. 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.

6.4.1 Economic analyses

This will be an incremental cost-effectiveness analysis of the EC intervention with passive UC intervention in comparison to the active UC intervention. There are three main components of data collection for the cost-effectiveness analysis.

Firstly, the costs of providing the EC intervention will be recorded and includes the costs of staff training, staff time for intervention delivery (including overheads), and of the EC products provided. We will collect costs prospectively alongside the cRCT in monetary form for direct expenses, and in terms of quantities for resources and apply local unit costs to the quantities of each resource utilised. We will also record the costs of providing UC.

Secondly, following NICE guidance (21), health care utilisation data will be collected. We will record health care utilisation data for contacts with the NHS and personal and social services (PSS) using a bespoke service use questionnaire which will incorporate revisions informed by the data from the feasibility study. This includes the use of primary and secondary health care services and social care. Quantities recorded are multiplied by national average unit costs (22,23) to derive a cost profile for each patient in each arm of the trial. The service use questionnaire will also include brief questions on patient's out of pocket expenditure on cessation aids, costs of travel to health services and lost productivity.

Thirdly, EQ-5D-5L (24) will be administered at each follow up. The EQ-5D-5L responses will be used to derive utility values and Quality Adjusted Life Years (QALYs) will be then calculated with these utility values using the area under the curve approach (25) based on a linear change between observations. The validity of the current EQ-5D-5L UK population tariff has been challenged and will therefore use the methodology recommended by NICE at the time of analysis to calculate QALYs which will be the primary outcome for the economic evaluation (23,25).

Intervention and health care costs are combined with QALYs to estimate the incremental cost per QALY of the EC intervention with passive UC comparing to active UC intervention at the primary endpoint from an NHS/PSS perspective. Underlying 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. We will perform the bootstrap 5000 replications and construct the 95% confidence intervals for the ICERs based on the bootstrapping results. Cost-effectiveness acceptability curves (CEACs) will be constructed based on the bootstrap iterations (27) to estimate the probability that the intervention is cost-effective at different threshold values for one QALY. We will also present a secondary analysis using the cost per quitter at the primary endpoint from an NHS and PSS perspective and a societal perspective (including patient cost of buying cessation aids, travel and productivity).

In addition to addressing the uncertainty surrounding the point estimate of the ICER, sensitivity analysis is undertaken to assess the effect of missing data. In the main analysis, missing data will be imputed using Rubin's multiple imputation method (28). As part of the sensitivity analysis, we will conduct a complete case analysis (CCA) whereby results are analysed only for those participants who had both the completed cost and outcome data at the same time. The missing at random assumption for multiple imputation will also be assessed using the methods recommended by Faria and colleagues (29).

The cost-effectiveness analysis will further use an existing model, with adaptations, to extrapolate the longer-term cost-effectiveness (26). The model is a three-state Markov model: former smoker, current smoker and death and was originally constructed for an SMI population. It takes into account age, gender, lifetime relapse rate, incidence of smoking-related diseases and their smoking-attributable costs, and QALYs. The basic model assumptions are generic and fit all populations. The model parameters could be adapted to fit other populations if required and we will adapt the model to fit the trial population based on evidence available (30). Trial data is combined with secondary data to estimate lifetime QALYs and cost per QALY gained from the NHS/PSS perspective as per NICE guidance and will therefore only use NHS and PSS costs and will not incorporate patient costs which are not relevant to this perspective. Uncertainties will be assessed using probabilistic sensitivity analysis and presented in the form of CEACs.

6.4.2 Process evaluation

The process evaluation will use both quantitative and qualitative approaches to explore treatment context, fidelity of implementation, mechanisms of change 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.

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

7 Data Handling & Record Keeping

7.1 Confidentiality

Only study personnel will have access to study data. We will not request any patient identifiable data or medical information about participants from their other doctors (hospital or general practitioner, GP).

All information will be kept confidential. After the study appointment, the researcher will upload all data (excluding personal data) onto REDCAP. Copies of all documents regarding the study will be kept in the trial master file (TMF) and/or relevant site file. Participants will be assigned a trial ID number.

7.2 Study Documents

- A signed protocol and any subsequent amendments
- Current/Superseded Participant Information Sheets (as applicable)
- Current/Superseded Consent Forms (as applicable)
- Current/Superseded Debrief Forms
- Study Advertisements
- Indemnity documentation from sponsor
- Conditions of Sponsorship from sponsor
- Contract with the NIHR
- Collaboration Agreement
- Documentation relating to adoption into the CRN portfolio
- Ethics submissions/approvals/correspondence
- CVs of PIs, TM, AL and RAs
- GCP certificates
- Schedule of responsibilities / delegation log
- Data flows
- Participant identification log
- Screening log
- Enrolment log
- Risk Assessments
- Current/Superseded Logic Model
- Correspondence relating to the trial

7.3 Case Report Form

Trained research assistants in each area will be responsible for ensuring the correct sections are completed at the relevant time-points throughout the study. All completed CRFs will be reviewed and signed off by the area leads

7.4 Record Retention and Archiving

All information relevant to the study will be archived and retained for at least 10 years at London South Bank University (unless otherwise specified). Consent forms, paper CRFs and participant contact details files will be kept securely at study sites until the end of the study and then transferred securely to LSBU. Participants contact details (personal details) will be kept securely for 2 years from the end of the study (see Figs. 2 & 3 data flows). Electronic data (which will not include participants' personal data) will be kept on a secure online database at LSBU and made freely available on openresearch.lsbu.ac.uk for at least 20 years. The sponsor will be informed in writing when and where all data is archived.

Figure 2: Data flow – main effectiveness and cost-effectiveness data

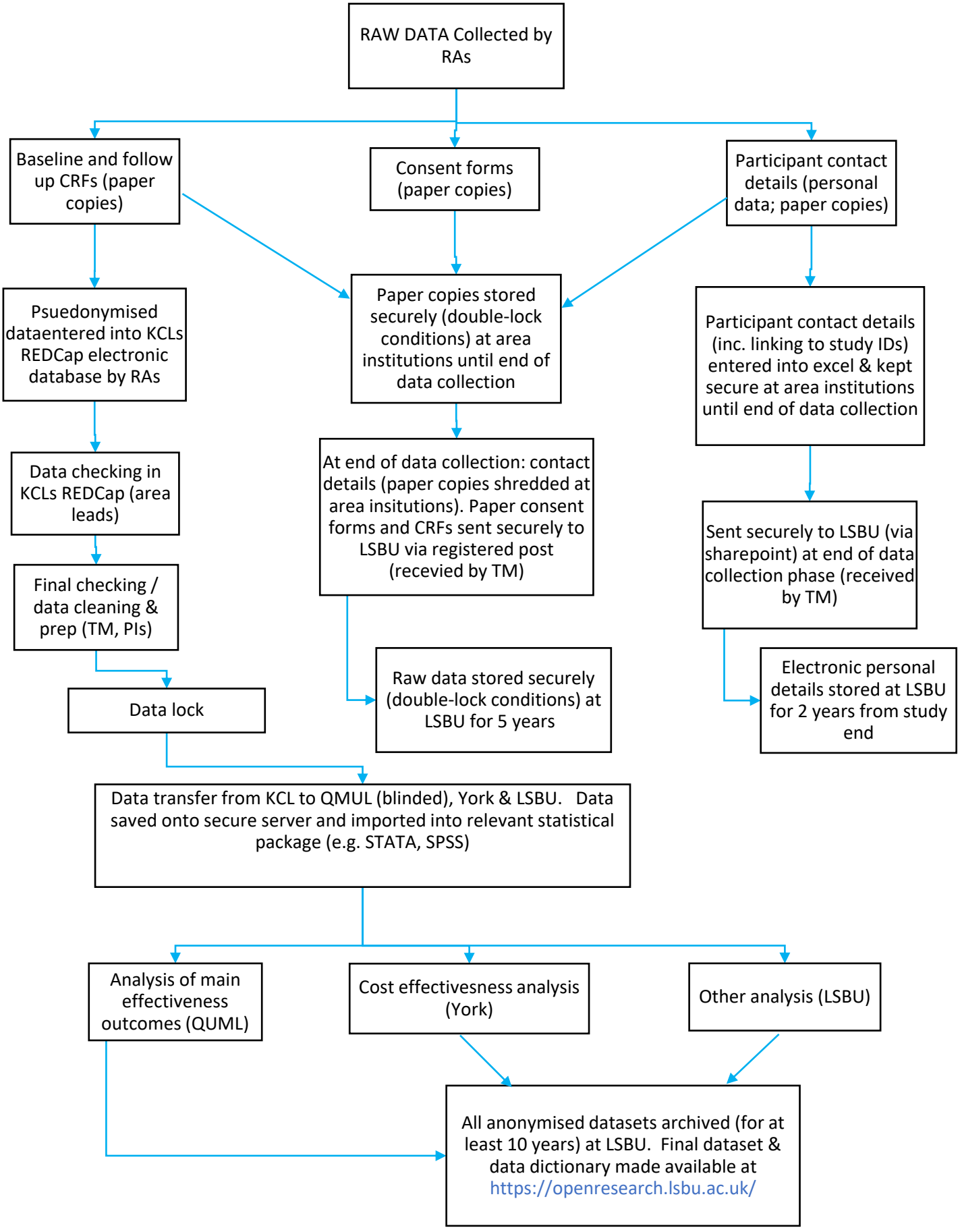
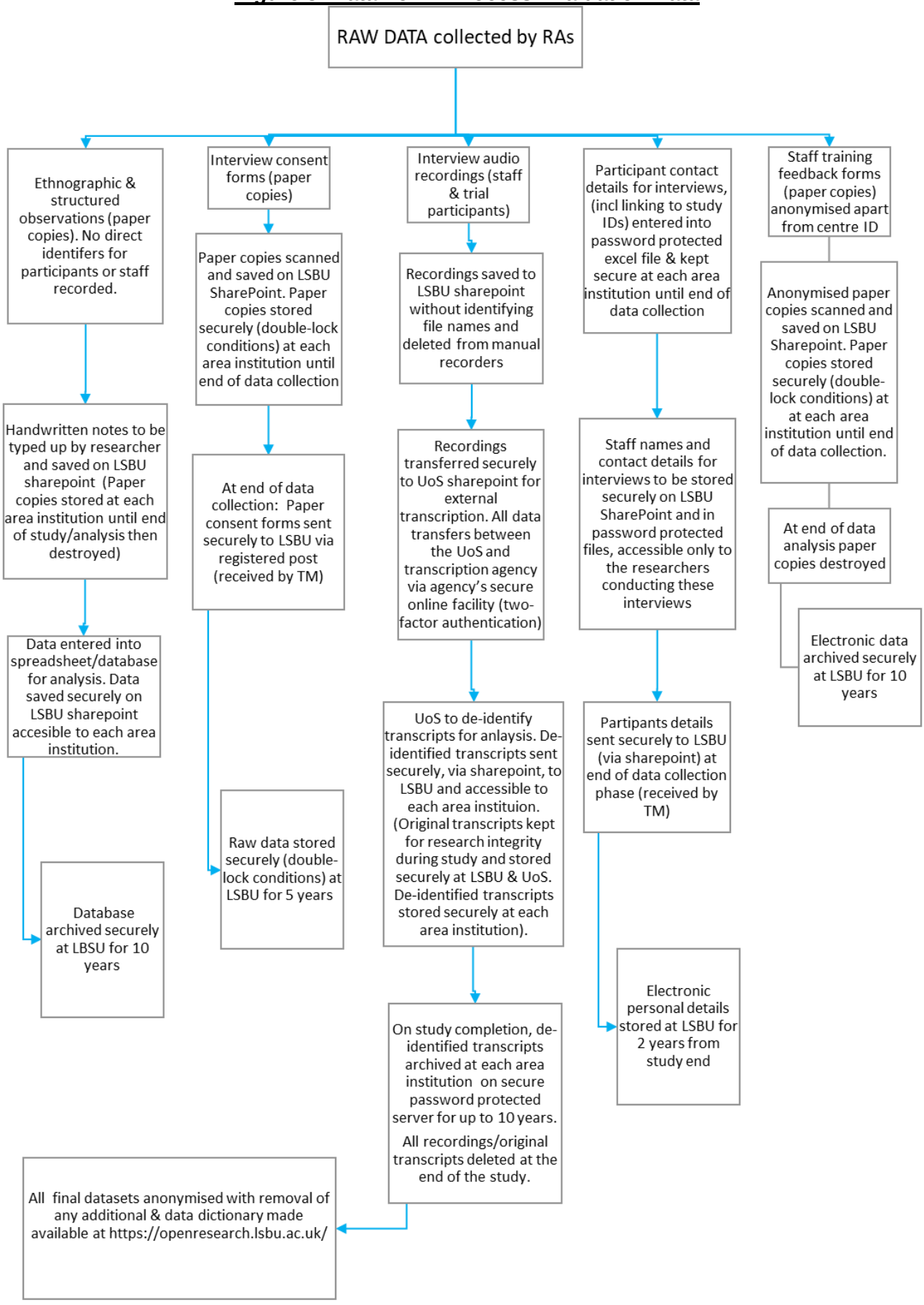


Figure 3: Data flow – Process Evaluation Data



7.5 Compliance

The TM, CI and area leads will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, sponsor's policies and procedures and any subsequent amendments.

7.6 Clinical Governance Issues

7.6.1 Ethical Considerations

This protocol and any subsequent amendments, along with any accompanying material provided to the participant in addition to any advertising material will be submitted by the Principal investigator to the Research Ethics Committee/Research and Enterprise Management System (HAPLO).

7.7 Quality Control and Quality Assurance

7.7.1 Risk Assessment

The study will be risk assessed by the PIs/TM and signed off by the LSBU Health, Safety and Resilience (HSR) Team in accordance with LSBUs Health and Safety Policy. In addition, each homeless centre site will be risk assessed by the area leads using the standard LSBU risk assessment template before recruitment begins at that centre. These risk assessment documents will be signed off by the TM and a copy of all risk assessment documents will be kept in the TMF.

7.7.2 Study Monitoring

Records relating to participant consent, recruitment and follow up will be kept on REDCap. Monthly recruitment and follow up figures will be kept in the TMF and reported to the NIHR via the NETSCC-MIS by the TM. Data from CRFs entered in REDCap will be monitored by area leads who will be responsible for checking 10% of the entries in their area. An interim report at the end of the pilot study will be produced for the TSC and funder who will review recruitment and follow up figures against the study stop/go criteria and advise on progression of the trial.

Table 2: Stop-Go Progression Criteria

Recruitment	Criteria	Action
90%	Go	Continue with trial
60-90%	Amber	Action plan to TSC & funder and formally reassess recruitment again at 12 months
<60%	Rescue Plan*	Rescue plan considered by TSC and funder and decide whether to continue

7.8 Audit and inspection

The investigator will permit study-related monitoring, audits, and inspections by the Ethics Committee, the sponsor, government regulatory bodies of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.).

7.9 Reporting of Serious breaches in GCP or trial protocol

All breaches and potential breaches in GCP or trial protocol will be logged by the area leads and reported to the PI or TM within 24 hours. The PI/TM will be responsible for reporting these to the REC/sponsor and the NIHR (via the incident reporting form) within 24 hours of becoming aware of the event.

7.10 Trial Committees

A Trial Steering Committee (TSC) and a Data Monitoring Committee (DMC) will be convened. The TSC will meet twice per year, the DMC once per year. A Trial Management Group (TMG) comprising the CIs, TM and area leads will meet monthly to communicate and monitor progress of the trial and address any problems arising.

7.11 Publication Policy

Study results will be written up for submission to international conferences and peer reviewed journals. No participant will be identifiable from any publication or report. We will also provide public and participant lay outputs.

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