E-cigarettes for Smoking Cessation And reduction in People with mEntal illness (ESCAPE trial)

TRIAL PROTOCOL

Version: 3.0

Date: 21st September 2021

Funder: Yorkshire Cancer Research

GENERAL INFORMATION

SPONSOR

The University of York is the trial sponsor. Queries relating to sponsorship should be addressed to: Michael.barber@york.ac.uk

FUNDING

This trial is funded by the Yorkshire Cancer research

AUTHORISATION AND APPROVALS

This trial will be submitted for approval by the Health Research Authority, Research Ethics Committees (REC).

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

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Name (please print):

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Position:

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Chief Investigator:

Signature: Date:

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Name: (please print):

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LIST of CONTENTS

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Committees	Contact details for TSC and DMC to be included here

STUDY SUMMARY

Study Title	E-cigarettes for Smoking Cessation And reduction in People with mEntal illness (ESCAPE trial)
Internal ref. no. (or short title)	ESCAPE trial
Study Design	Phase I is a randomized controlled feasibility trial with an embedded process evaluation, comparing the intervention (e-cigarette starter kit as an adjunct to usual care) and control groups (usual care) at 1-month follow-up. Phase II, full RCT - similar approach to the feasibility trial with a follow-up point at 6 months.
Study Participants	Participants will include adults (> 18 years) currently receiving treatment for a mental illness under the care of secondary care psychiatric community teams or community mental health teams (CHMTs) at three Northern Mental Health Trusts.
Planned Size of Sample (if applicable)	The target sample size for the randomised controlled feasibility trial is 72, with 36 participants allocated to each group.

	For the full trial, a sample of 740 participants (370 per group) would provide 80% power, with alpha=0.05 in two-tailed analysis.
Follow up duration (if applicable)	Phase I - 1-month follow-up. Phase II - 6-month follow-up.
Planned Study Period	Randomized controlled feasibility trial (Phase I; months 1-12), fully powered RCT (Phase II; months 13-48)
Research Question/Aim(s)	The main aim is to assess the effectiveness and cost-effectiveness of providing an e-cigarette starter kit to people with mental Illness (PWMI) treated in the community to aid smoking cessation and harm reduction, as an adjunct to 'usual care'. The objectives of the proposed research are: 1. To test the feasibility and acceptability of the intervention and research processes in a randomized controlled feasibility trial (Phase I). 2. Based on findings from objective 1 and following potential refinement of intervention content and delivery, to assess the clinical and cost-effectiveness of the intervention for smoking cessation and harm reduction (Phase II).

FUNDING AND SUPPORT

FUNDER(S)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
Yorkshire Cancer Research	Financial Support
NIHR Clinical Research Network (CRN)	Non-financial – Study support service

ROLE OF STUDY SPONSOR AND FUNDER

The Sponsor

The sponsor of the trial is the University of York. The University of York holds insurance against claims from participants arising for negligent design and trial management for injury caused by their participation in this clinical trial (see section 7 on indemnity for more information).

The funder

Financial support for the trial has been provided from Yorkshire Cancer Research. Yorkshire Cancer Research have had no influence on the study design and will have no influence on the data collection and analysis of the feasibility trial or the main trial. NIHR Clinical Research Network (CRN) will provide non-financial support for the planning and set-up of the trial. CRN funded researchers will assist with the early stages of the trial.

NIHR CRN have had no influence on the study design and will have no influence on the data collection and analysis of the feasibility trial or the main trial.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial Steering Committee

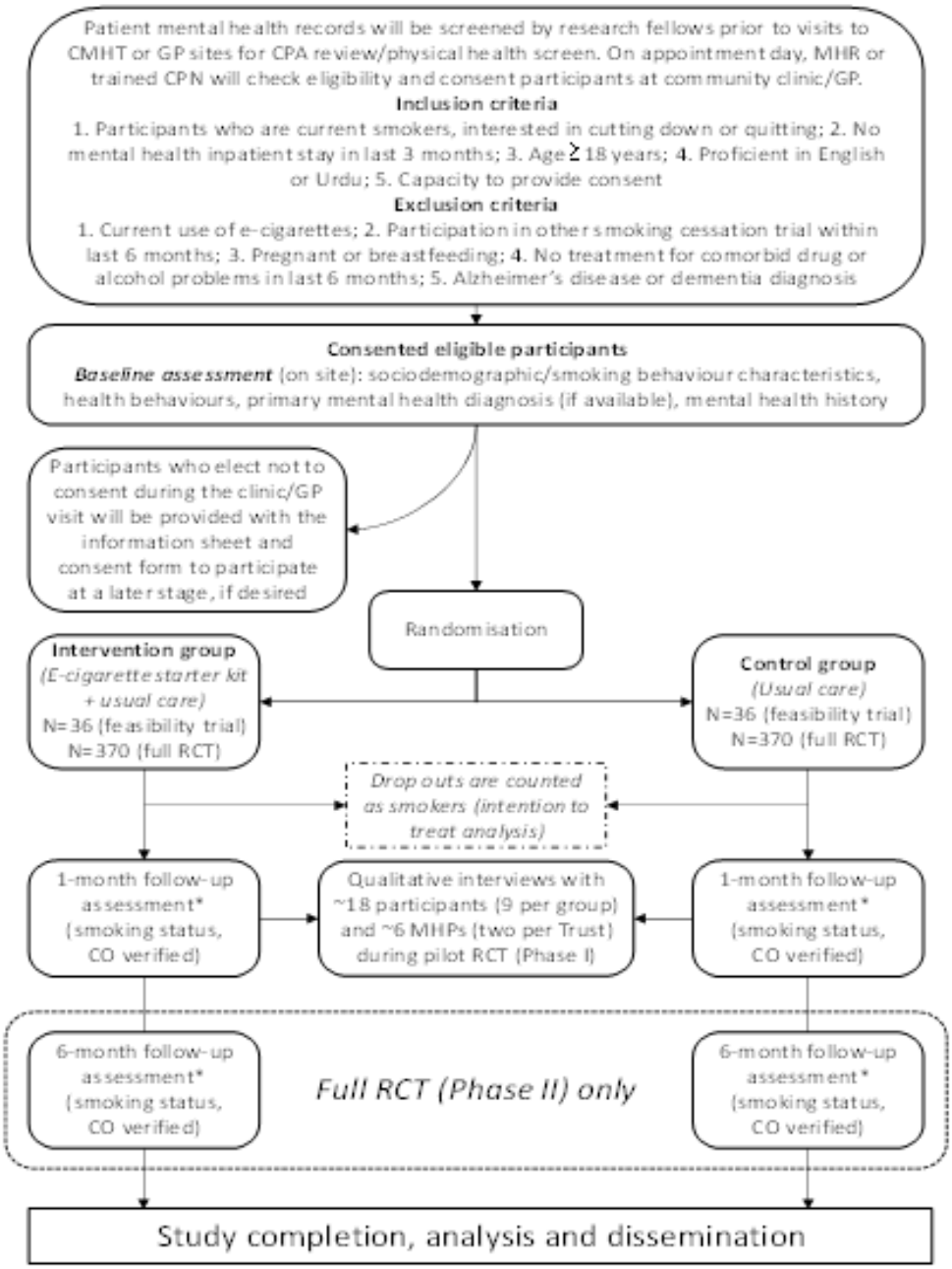
Trial Steering committee membership to be confirmed - Within the first two months of the project start, we will appoint independent members to the TSC and DMC with oversight over both the feasibility and full RCT. The TSC will include a chair, clinicians, patient representatives, behavioural scientists, health psychologists, statisticians and health economists. The DMEC will comprise a medical doctor as chair and include experts in the field of tobacco control with experience of running large RCTs.

Patient & Public Involvement Group

The project will be supported by service users with lived experience of mental illness and smoking in the following ways: Brothers Phil and Simon Hough, a service user with severe mental illness and his carer (both ex-smokers), who are named co-applicants and centrally involved in its design from an early stage. In addition, we will convene a project-specific PPI group, recruiting patients and carers with interest in research from the participating Trusts' service user groups, utilising close contacts we have established in the context of previous research (including the recent SCIMITAR trial, led by Prof Simon Gilbody, also a co-applicant). We estimate that our PPI group, which will be facilitated with support from Phil and Simon Hough, will have approximately six members from Yorkshire. Further PPI involvement will be facilitated and supported by our collaborators: Action on Smoking and Health (ASH) and a mental health charity (Equally Well).

The project relies on PPI involvement at all stages. PPI representatives from our core project team (Phil and Simon Hough), our project-specific PPI group and charity collaborators (Equally Well at The Centre for Mental Health) will be consulted approximately every four months (more frequently if required) and involved in co-production activities as research progresses. Complexities in this area, which include the heavy tobacco addiction experienced by many mental health service users, call for an approach that supports maximal service user orientation for the development of a relevant, acceptable and successful intervention. PPI representatives will be involved in the planning of the research, the development of service user-oriented intervention and research materials (e.g. leaflet), aspects of research conduct (e.g. development of topic guides for qualitative interviews in the pilot trial), networking with existing PPI groups nationally, and dissemination activities with a focus on informing national policy in this area.

STUDY FLOW CHART



**From enrolment or target quit date (whichever is later; participants are given a week's grace period to set their quit date), carried out at community/GP clinic or at participant home; CMHT – Community Mental Health Team; GP – General Practitioner; CPA – Care Programme Approach; MHR – Mental Health Researcher; CPN – Community Psychiatry Nurse*

ABREVIATIONS

Abbreviation	Expansion
AE	Adverse Event
BCT	Behaviour Change Technique
BDCT	Bradford District Care Trust
CMHT	Community Mental Health Team
CPA	Care Programme Approach
CPN	Community Psychiatric Nurses
CRF	Case Report Form
CSO	Clinical Studies Officer
CTU	Clinical Trials Unit
e-cigarette	Electronic cigarette
ICER	Incremental Cost Effectiveness Ratio
MHR	Mental Health Researcher
NRT	Nicotine Replacement Therapy
PPI	Patient and Public Involvement
PWMI	People With Mental Illness
QALYs	Quality-Adjusted Life Years
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SMI	Severe Mental Illness
SSS	Stop Smoking Services
SUTS	Strength of Urges To Smoke
TEWV	Tees, Esk and Wear Valleys NHS Foundation Trust
VBA	Very Brief Advice
YCR	York Cancer Research

1. BACKGROUND

Tobacco smoking remains the leading preventable cause of death and disease in England and is responsible for around 78,000 deaths annually [1], posing a financial burden of almost £3 billion to the NHS [2]. Despite smoking prevalence in the UK general population declining steadily over five decades, now standing at ~15% [3], no change has been observed among people with mental illness [4, 5]. With an average smoking prevalence of 40%, people with mental illness (PWMI) are more than twice as likely to be smokers as the general population [5], although smoking rates in this population can reach figures of up to 70% in subgroups such as hospitalised patients with severe mental illness (SMI)[5, 6]. Combined with high levels of nicotine dependence [7] which result in generally high cigarette consumption, this leads to substantially increased risks of smoking-related morbidity and premature mortality in PWMI [5], where up to 20 life years are lost largely to diseases related to smoking such as lung cancer, the biggest contributor to health inequalities [8].

Although PWMI are similarly motivated [9] and able [10] to quit smoking to those without mental illness, standard stop smoking services (SSS) are not commonly accessed by this population [11, 12], and are decreasingly resourced to support the need of smokers with SMI for tailored support [13-15]. Strong evidence that quitting smoking improves rather than exacerbates symptoms of mental illness [16], and may be causally linked to the development of mental illness [17] only emerged in recent years. Smoking until very recently remained deeply embedded in the culture of UK mental health settings [18], where it was commonly accepted as a coping mechanism for patients [5, 19, 20]. The 2013 joint Royal College of Physicians/Royal College of Psychiatrists report [5] and NICE guidance (PH48) [21] draw attention to the need to address this 'smoking culture'. The NICE guidance recommends that all mental health settings be entirely smoke free without exemption, with no facilitated smoking breaks, and evidence-based tobacco dependence treatment for smoking cessation, harm reduction and support for temporary abstinence available to all patients who smoke [21]. In line with goals of the *Tobacco Control Plan for England* and the *NHS Long Term Plan* mental health Trusts across the country are currently in the process of implementing the guidance, with evaluations underway [22, 23].

For many PWMI, contact with health professionals presents a 'teachable moment' [24] with opportunities to address smoking [25]. Research shows that opportunities to support smoking-related behaviour change could be better used in both inpatient [26] and community mental health settings [27]. The importance of developing smoking cessation interventions that are more effective than existing standard treatments for PMWI has been highlighted in various policy documents [21, 28, 29].

One of the largest smoking-related trials conducted among community patients with Severe Mental Illness (SMI), demonstrated that patients with SMI can successfully quit if intervention content is tailored to their needs [30]. SCIMITAR included existing evidence-based pharmacological and behavioural support but did not include any supported use of e-cigarettes (as these emerged only after the project had been designed). The smoking cessation-related support that was delivered by mental health practitioners more than

doubled quit rates at 6 months. In the context of NICE guidance PH48, mental health Trusts are now moving towards the kind of smoking cessation-related support provision that was tested in SCIMITAR, with results of this trial substantially influencing clinical practice. However, the design of the SCIMITAR study did not fully embrace the potential benefits of e-cigarettes in PWMI, described below.

E-cigarettes are popular; in England use by smokers and recent ex-smokers currently stands at around 20% and around 30% used e-cigarettes in quit attempts in 2021, compared with 3% of smokers accessing SSS [31]. E-cigarette use is increasingly being recorded by SSS [32], and appeal in particular to PWMI who are more likely to have tried e-cigarettes and be current users than smokers in the general population [33]. There are several reasons for this. Firstly, e-cigarettes are relatively cheap compared with both cigarettes and other cessation treatment [34]. Second, they offer a simple stand-alone treatment that is intuitive to use. Third, since e-cigarettes simulate the sensory input from cigarettes and allow users to control the dose (unlike most NRT), they may appeal to more dependent smokers who have hitherto struggled to quit, with the potential to enhance existing cessation treatments and replace combustible tobacco products [35]. Thus e-cigarettes may be one solution to reduce smoking and encourage cessation in mental health care settings by functioning as a safer alternative to cigarettes [36].

In the general population, more and more evidence is accumulating to show that e-cigarettes are at least as effective a smoking cessation aid as NRT, both from randomised controlled trials (RCTs) [37-40] and real-world studies [41, 42]. In addition, there are small observational studies, which support their use for PWMI. Work carried out in Italy [43], the US [44] and Australia [45] found that e-cigarettes are effective for smoking cessation and reduction among smokers with SMI. More recently, a UK-based pilot study reported a significant reduction in average number of cigarettes smoked per day ($\geqslant$ 50%) between baseline and 6-week follow-up, supporting the notion of e-cigarettes as a potentially successful harm reduction intervention for smokers with psychotic disorders [46]. These studies did not report any adverse effects for mental health, underlining the utility of e-cigarettes as a tobacco harm reduction product for smokers with SMI. However, while these preliminary results are encouraging, to date no adequately powered RCT has assessed the effectiveness of e-cigarettes as a long-term ($\geqslant$ 6 months) harm reduction and smoking cessation tool in everyday practice. This project therefore aims to assess the clinical and cost-effectiveness of the offer of an e-cigarette starter kit as an adjunct to usual care, compared with usual care alone, in a pragmatic RCT of PWMI treated in the community.

2. AIM AND OBJECTIVES

Our main aim is to assess the effectiveness and cost-effectiveness of providing an e-cigarette starter kit to PWMI treated in the community to aid smoking cessation and harm reduction, as an adjunct to 'usual care' incorporating both a randomised controlled feasibility trial (Phase I; months 1-12) and a fully powered RCT (Phase II; months 13-48). This includes an embedded stop point after Phase I. The objectives of the research are:

1. To test the feasibility and acceptability of the intervention and research processes in a randomised controlled feasibility trial (Phase I).

2. Based on findings from objective 1 and following potential refinement of intervention content and delivery, to assess the clinical and cost-effectiveness of the intervention for smoking cessation and harm reduction (Phase II).

3. PHASE I – RANDOMISED CONTROLLED FEASIBILITY TRIAL (MONTHS 1-12)

3.1. Aim

We aim to conduct a randomised controlled feasibility trial of an e-cigarette starter kit (4-week supply and leaflet) as an adjunct to usual care for smokers with mental illness treated in the community.

3.2 Study objectives

3.2.1 Primary research objective: to assess the feasibility and acceptability of the e-cigarette-based intervention and associated research processes in our study population, establishing central parameters for the design of a definitive RCT (Phase II), including recruitment and retention rates.

3.2.2 Secondary research objectives: (1) to determine whether progression to a full trial is reasonable, based on the confidence interval approach [47] (see also 1.9); (2) to establish e-cigarette adherence rates and potential level of contamination between study arms to inform planning for a full trial; (3) to assess fidelity of intervention delivery; (4) to establish the feasibility of data collection and training procedures and pilot the gathering of cost data to inform methods for health economic analysis in Phase II; (5) to explore barriers and facilitators to participation; (6) if indicated, to refine the intervention and study protocol in readiness for a full RCT.

3.3 Study design

Phase I will consist of a randomised controlled feasibility trial with an embedded process evaluation, comparing the intervention (e-cigarette starter kit as an adjunct to usual care) and control groups (usual care) at 1-month follow-up.

3.4 Treatment groups

3.4.1 Intervention group - E-cigarette starter kit as adjunct to usual care

The intervention group will be offered an e-cigarette starter kit, compliant with EU regulation, and an information leaflet about e-cigarettes, in addition to usual care. Usual care differs between (and sometimes within) Trusts but is guided by NICE guidance PH48 [48], with a minimum standard of evidence-based very brief advice (VBA) to stop smoking, comprising the three As: Ask and record smoking status; Advice on the best way of quitting and Act on patient response to build confidence, and referral to in-house or external specialist stop smoking services.

The e-cigarette starter kit containing an e-cigarette a four-week supply of e-liquid and an information leaflet will be provided to participants in the post for those on the online pathway (pathway 1 – will be sent a letter with instructions not to start using this until after the intervention) and in person at their appointment for those on pathway 2 (see 3.6.3). A third-generation e-cigarette with a refillable tank from a tobacco industry independent manufacturer will be offered, for example the Aspire PockeX, which was used in a recent trial that provided evidence of a superior effect of e-cigarettes over standard nicotine replacement therapy [49]. There is good evidence that these products are more effective in delivering nicotine than others [50].The choice of e-liquid will be based on the most popular flavour and concentration combinations in the UK [51].

Participants of the feasibility trial in Phase 1 will be provided with a selection of different flavours (tobacco, fruit, and menthol) as well as different concentrations (Concentrations offered will vary between 6 mg/ml to 20 mg/ml) to allow them to experiment and select their preferred choice of flavour/nicotine concentration combination. This will also help us establish preferences in this patient population for the full trial in Phase II to minimise negative responses to using the e-liquid. In addition, advice on the use of e-liquid and encouragement to contact the research team by email or telephone if the liquid is not accepted well will be provided for the full trial in Phase II where participants can choose only one of several flavour/nicotine concentration combinations. Participants who perceive the e-liquid to be aversive will be posted replacement e-liquid.

At a scheduled appointment with a clinician, a brief consultation will be conducted with participants to provide necessary instructions for use of the kit. This appointment can be an online if this is usual practice for those on the online pathway. All participants will be encouraged to consider quitting and to set a target quit date within a week. As set quit dates are likely to vary widely and may change over time, all participants will have a two week 'grace period' from enrolment to decide whether they chose to set a target quit date or not. Participants will be asked to start using the e-cigarette when they quit and to seek out local vape shops to obtain further e-liquid, suited to their individual needs and flavour preference. Participants who do not wish to set a target quit date will be encouraged to use the e-cigarette to reduce cigarette consumption as soon as possible.

3.4.2 Control group - Usual care

The control group will receive care as usual, as outlined above. As is common practice in pragmatic 'real-life' trials that involve variations of 'usual care' across organisations and localities, we will record the characteristics and details of usual care provided at each site to take these into account in the analyses and will codify treatment content in both groups using a well-established behaviour change taxonomy commonly used in tobacco research [52].

3.5 Randomisation and allocation concealment

The intervention allocation will be determined by block computer-randomisation to ensure that each trial site has an equal proportion of intervention and control group participants. Those on the online pathway (pathway 1; see 3.6.3) will be informed electronically via email and those on the paper-based pathway (pathway 2; see 3.6.3) will

open a sealed envelope at their appointment. Randomisation will occur after consent to take part in the study has been obtained. Due to the nature of the intervention, it will not be possible to blind participants or all researchers to treatment allocation. The lead applicants, co-applicants, and statisticians, however, will be blinded.

3.6 Participants and procedures

3.6.1 Participants

Participants will include adults (> 18 years) receiving treatment for a mental illness under the care of secondary care psychiatric community teams or community mental health teams (CMHTs) at three Northern Mental Health Trusts (see 3.7). Smokers (who smoke regularly and have smoked combustible cigarettes in the past 7 days) with any mental health condition will be eligible to participate. However, to reduce the possibility of hospital admission for acute events (and thus the risk of drop-out), patients must not have had an inpatient admission in the last 3 months according to their health care record. Participants must be willing to address their smoking behaviour, either by attempting to quit or by reducing their consumption and have capacity to provide consent. Smokers who are currently using e-cigarettes regularly (at least weekly), are participating in other smoking cessation trials, are being treated for comorbid drug or alcohol problems, have a diagnosis of Alzheimer's disease or dementia, or are pregnant or breastfeeding will be excluded. Reasons for exclusion and, for eligible patients, reasons for non-participation will be documented where possible/provided.

3.6.2. Recruitment

Each Trust will be allocated a part-time dedicated MHR to support project delivery in the respective localities. Patients with an appointment planned in the coming weeks will be invited to part by letter, which will be sent from the patient's mental health team, or GP surgery for primary care patients. A follow-up call or text will be sent after 7 days.

3.6.3 Procedure

Participants from Mental Health Trusts (Secondary Care) will be identified via health records prior to attendance at an up-and-coming appointment. A list of potential participants will either be checked for smoking status by clinical studies officers (CSOs) or a care coordinator/other appointed person at a GP surgery for primary care. Participants who smoke will then be contacted by letter containing the participant information sheet in advance of their appointment to ascertain interest in the study and may also receive a follow-up call to check they have received the letter. Those who are interested will be asked to respond to indicate this either verbally over the telephone, by advice slip in the post or using an online link. They will then receive a call from the research team to check eligibility using the checklist and answer questions which participants have relating to the study. If interest in participation is confirmed informed consent will be sent electronically (pathway 1). There will also be a paper-based option available for those who do not wish to use the electronic option. In this case, participant information and consent forms will be given in person at a scheduled appointment.

Eligible, consented participants will be asked to complete a brief baseline questionnaire, which will be administered via GDPR-compliant online survey tool REDcap (or in person at the same scheduled appointment as consent, which will require the participant to attend their appointment 30 minutes early to meet with the CSO) assessing sociodemographic and smoking behaviour characteristics, with mental health diagnosis and history being obtained from health care records. For those following the online pathway, once a participant has completed and returned the baseline assessment materials, a link will be sent to the participant to inform them of which group they have been randomised to. For those on the paper-based pathway this will be done in person via a sealed envelope (randomisation will have been generated prior to this by computerised block randomisation at the UCL Clinical Trials Unit see 3.4). At this stage, interaction with participants allocated to the control group will stop to allow them to attend their appointment and receive care as usual. Participants allocated to the intervention group will also attend their appointment and receive care as usual but in addition will receive the e-cigarette starter kit, a leaflet and brief explanation (see 3.5.1).

Follow-up of participants at 1 month in phase 1, and at 1 and 6 months in phase 2, will be undertaken by dedicated mental health researchers. Follow-up surveys will be completed via telephone with an option to receive this by post if preferred. In-person follow up at CMHT sites or participants' homes will be required to biochemically validate self-reported abstinence only through carbon monoxide readings (likely to affect approximately 12 participants in phase 1, and 94 participants in phase 2 as per expected abstinence in control and intervention arms in both the feasibility and full trial; see subsections 3.9 and 4.6 of the submitted application). Figure 1 shows a flow diagram of the participant journey through the study. For COVID-19 risk management, social distancing and hygiene measures will be strictly observed and the study team and participants briefed in advance of the follow up visit. Individual mouth pieces for the monitors will be discarded immediately after use and the monitor core piece disinfected. Staff and participants will be provided with PPE – surgical face masks and plastic gloves.

3.6.4 Procedural variations

During Phase I, we will also pilot two procedural variations at selected sites to determine the scalability of the intervention for Phase II. First, to account for the overrepresentation of some ethnic minorities in the study population, materials (including leaflets, questionnaires, participant information sheets etc.) will be available in both English and Urdu and the intervention delivered by a bilingual MHR at specific sites to allow PWMI with limited English to participate in the study.

3.7 Trusts and study sites

Three Trusts will be involved in phase I: Tees, Esk and Wear Valleys NHS Foundation Trust (TEWV –the largest mental health Trusts in England) will be the host Trust. TEWV has numerous sites across Yorkshire. Bradford District Care Trust (BDCT) will also include a minimum of two sites. TEWV and Bradford will recruit from secondary care. SHSC/Sheffield CCG will facilitate recruitment in primary care sites only. SHSC/Sheffield CCG will approach 2-3 primary care networks to participate in Phase I and increase this to

all (15) networks for Phase II. All trusts have substantial experience with facilitating stop smoking research and support infrastructure is already in place, having recently been involved in the successful delivery of the SCIMITAR+ trial [30].

3.8 Measures

3.8.1 Baseline measures

Baseline measures will be collected via a brief questionnaire and health records.

3.8.1.1 Socio-demographic characteristics: These include age, sex, employment status, ethnicity, education, employment, accommodation type and marital status.

3.8.1.2 Smoking-related characteristics: These include general smoking characteristics, quit attempts and methods (including e-cigarettes), nicotine dependence [53], strength of urges to smoke (SUTS) [54], motivation to quit [55] and adexhaled breath carbon-monoxide (CO) reading.

3.8.1.3 General and mental health-related characteristics: These include most recent diagnosis (if available), antipsychotic medication use, and acute events (e.g. hospitalisation) in the last year. Mental health symptoms will be assessed with the PHQ-9 [56], GAD-7 [57] and SF-12 questionnaires [58].

3.8.1.4 Health behaviour characteristics: Alcohol use [59], exercise [60] and diet [61] will be assessed.

3.8.2 Primary outcome measures:

3.8.2.1 Feasibility and acceptability outcomes: The primary feasibility outcome measures in the feasibility trial will be consenting rate and recruitment frequency. Consenting rate will be calculated from the number of eligible participants approached who consent to take part in the study. The criterion to judge whether a large-scale RCT is feasible using the proposed recruitment approach is consenting a minimum of ~15% of eligible participants (see 3.14) which is slightly lower than the consenting rate typical in clinical trials in general patient populations in the UK [62]. Recruitment frequency will be calculated as the number of eligible patients at each site who agree to participate in the trial per month. Based on our projection of the number of participating trusts and sites in the full RCT, we would require around six participants per month from each Trust to deliver the full RCT successfully (see 3.9/4.4). MHR (or CPN) will be asked to record the number of non-eligible patients using a check list of common reasons for exclusions.

The acceptability of the intervention and research procedures will be investigated using a short proforma based on the Theoretical Framework of Intervention Acceptability [63], provided to all participants at follow-up. This will be complemented by qualitative interviews conducted with a sample of approximately 18 participants from the intervention and control group (including, wherever possible, those who disengaged during the course of the study). We will gain insights into patients' experience with the intervention and barriers to and facilitators of success, both in terms of the intervention content and the research process. MHR (or CPN) delivering the intervention in each Trust will provide detailed feedback on their experience, and on barriers and facilitators to

delivery, through feedback diaries and interviews; in addition, in-depth qualitative interviews will be conducted with six MHR/CPNs (two from each Trust).

The attrition rate will be measured as the number of participants who fail to complete follow-up at 1 month. In order to ensure a sufficiently robust effect estimate, which can be affected by high attrition rates in intention to treat analyses [64], attrition rates should not exceed 30%, typical for smoking cessation trials in this population [65] (see 3.14). Reasons for withdrawal will be obtained, where possible. In addition, adherence to treatment (e-cigarette use) will be assessed at 1-month follow up.

3.8.2.2 Clinical (smoking-related) outcomes: This is the primary clinical outcome measure for the feasibility trial, assessed at 1-month follow up. Continuous abstinence will be defined as not having smoked in the two weeks prior to follow-up (weeks 5 and 6 from enrolment), verified by a CO reading below 10 ppm, in keeping with the standard measure used in Stop Smoking Services. This measure will be used to determine whether to progress to Phase II and a full trial, based on the confidence interval approach (see 3.9 and 3.14).

3.8.3 Secondary outcome measures:

3.8.3.1 Feasibility and acceptability outcomes: Fidelity will be assessed by randomly sampling two intervention sessions per site with trained staff, audio-recording them and coding the use of behaviour change techniques (BCTs) delivered during the session to determine the proportion of BCTs used compared to specification in the manual [66]. Characteristics of 'usual care' in different locations will be also noted, recording two interactions of patients with CMHTs or GPs at each site at baseline and using short pro-forma with control group participants at follow-up. While the nature of the intervention and delivery format means that contamination is unlikely to be a problem, qualitative exploration will be undertaken with 25% of control group patients to investigate in depth reasons for smoking behaviour change and identifying potential (unintentional) links with our intervention. Based on our findings, we will estimate the presence/extent of contamination in the control group, and the need to change the study procedure (e.g. spacing randomisation per site). Further, the feasibility of intervention delivery via CPNs and using both English and Urdu will be assessed by calculating the number of successfully trained CPNs in each Trust, their recruitment rate and fidelity of intervention delivery as well as the proportion of Urdu speakers successfully recruited into the trial. Participant burden of data collection will be asssessed via qualitative interviews conduction online or via telephone with particpants to assess acceptability, which forms part of our list of measures collected in the feasibility study (Phase 1) to determine stop/go decision for the Phase 2 full trial. Should this issue be raised as a barrier to participation, we will seek to prioritise which measures to retain in the full trial.

3.8.3.2 Clinical (smoking-related) outcomes: Self-reported abstinence 2-4 weeks from enrolment or target quit date (whichever is later) will be recorded at 1-month follow-up. The change in cigarette consumption (and reduction in exhaled breath CO reading) from baseline to 1-month follow-up will be calculated in both intervention and control group participants.

3.8.3.3 Clinical (mental health-related) outcomes: At 1-month follow-up, general and mental health functioning will be assessed as per baseline (see 3.8.1.3).

3.8.3.4 Cost effectiveness: We will pilot service use questionnaires for health economic analysis and assess the health care utilisation data returned. We will calculate the costs of delivering the intervention and the control condition as the basis for the full RCT, for which a cost-effectiveness analysis is planned.

3.8.3.5 Serious Adverse Events (SAE): Adverse events (AE) will be recorded at 1-month follow-up as part of the follow-up questionnaires participants complete. The data management committee, led by a medical professional, will act as independent reviewer to determine whether any event is likely to be related to the trial and whether or not it is expected. This will include any events that may be related to the use of nicotine. Structured data on any events or 'side effects' experienced by participants will be collected at 1-month follow-up. In addition, we will also request Trusts to provide ad-hoc data on any serious adverse events that are disclosed through standard reporting procedures within the NHS, i.e. self-notification.

An event will be classed as serious if it considered to be: life threatening (i.e., event in which patient is at risk of death at the time of the event occurring); fatal; requiring unplanned admission to hospital resulting in an inpatient stay or extension of hospital stay beyond what is expected (i.e., patient operated on as an outpatient but remains in hospital overnight); resulting in persistent or substantial disability or incapacity; resulting in a congenital abnormality; or any other medical condition not listed here that might require medical or surgical intervention to prevent the above criteria occurring. Should the data management committee deem a serious adverse event to be related to the trial, this will be reported to the REC immediately (within the required 15 days).

3.9 Power Calculation

The target sample size for the randomised controlled feasibility trial will be 72, with 36 participants allocated to each group. In a full RCT, we would assume an effect size of OR (odds ratio) of 3.9 (pooled estimate based on e-cigarette vs placebo e-cigarette trials: [38, 39]) for the primary clinical outcome (1-month continuous abstinence rate). This would result in an absolute predicted risk difference of 8.2%, assuming a 1-month abstinence rate in the control (usual care) group of 11.4% [based on EAGLES trial [67]] and 19.6% in the intervention (e-cigarette starter kit and usual care) group. The pilot sample size would be sufficient to produce a one-sided confidence interval that excludes an 8% difference in the event of a zero effect of the intervention on abstinence at 1 month, assuming 11% reported abstinence in each of the two groups. The estimate obtained in the feasibility trial will not be used to directly estimate the intervention effect (see 2.5) but to determine whether proceeding to a trial is worthwhile, based on the confidence interval approach [47].

In addition, the Phase I study is powered to detect clinically relevant within-subject changes in two secondary clinical outcome measures: cigarette and exhaled breath CO reductions. A recent study [8] in which smokers with mental illness, who were not intending to quit smoking, were provided with e-cigarettes showed that half of smokers

reduced their cigarette consumption by 50%. This e-cigarette supported level of reduction has been linked to a significant lowering in exposure to biomarkers of smoking-related harm [68]. Further, such smoking reduction in concert with provision of non-combustible nicotine delivery devices may aid future complete cessation [69]. The target outcome is therefore a reduction in cigarette consumption by at least 50% (or a 30% reduction in CO levels, common for smoking reduction of this magnitude [70]). Half the sample size in the intervention group (those expected to reduce consumption, n=18) provides 80% power to detect a medium- to large-sized effect (Cohen's d=0.7), reflecting a 50% reduction in cigarettes smoked per day from 12 to 6 cigarettes (average cigarette consumption based on population samples (e.g. [71]) and a 30% reduction in CO levels (from 18.5 to 13 parts per million (ppm); baseline estimate based on a opportunistically recruited population sample [72]).

Based on latest figures, it is estimated that involvement of two sites per Trust would reach around 100 patients per month per Trust. With smoking prevalence higher in this than in the general population, at around 40%, and with a conservative estimate of a consenting rate of around 15%, we therefore anticipate around six participants per Trust per month to be included in the feasibility trial, resulting in a total recruitment time of four months, with an additional month added as a buffer to account for uncertainty around the recruitment rate.

3.10 Analyses

The results of the feasibility trial (e.g., preliminary effectiveness, feasibility and acceptability) will determine whether a full RCT (Phase II) is viable. The primary outcome, smoking abstinence for weeks 2-4 from enrolment or target quit date (for those who set a date within one week of enrolment), assessed at 1-month follow-up will be descriptively analysed in line with the one-sided confidence interval approach [47]. Consenting rate, recruitment frequency as well as attrition and adherence rate will be calculated to determine feasibility and to decide which recruitment route is most effective. Qualitative data on acceptability will be analysed using Framework analysis, guided by the Theoretical Framework of Intervention Acceptability [63], to determine themes related to barriers and facilitators to intervention acceptability, and with thematic analysis [73] to explore interview data from trial participants and research and CMHT or allied mental health professional staff. We will also conduct a simple cost effectiveness analysis to determine incremental cost-effectiveness ratios for each additional quitter in the intervention compared with control group. Secondary clinical outcome measures will be analysed using generalised linear models (with intervention allocation specified as between-group factor and time as within-group factor) to determine reductions in cigarette consumption and exhaled breath carbon-monoxide readings and changes in mental health measures from baseline to 1-month follow-up. Fidelity will be determined using an established methodology of BCT-coded audio recording of intervention sessions [66]. Finally, for all quantitative analyses (primary and secondary outcome measures), Bayes Factors will be calculated to examine for non-significant results whether the associations indicated evidence of no effect or data being insensitive to detect an effect, and for significant results, the strength of evidence [74].

3.11 Phase I Milestones

Study 1 of the project will begin on 1st November 2021, running for 12 months. The time between the award decision and month 1 will be used to begin the relevant approval processes (e.g. NHS Research Ethics Committee), to apply for adoption onto the CRN portfolio and recruit research staff. Months 1-2 will be used to complete the study set up (including intervention training, acquisition of intervention materials, and setting up of Advisory/PPI group and trial committees). Recruitment into the feasibility trial and 1-month follow-up will take place between Months 3 and 8, including qualitative interviews. Qualitative analysis will start immediately and quantitative analysis at the end of follow-up in Months 8-10. The final two months will be used to write and submit a report to YCR (months 10-12). During this time, we will also begin to recruit the additional sites across Yorkshire, to follow up on discussions that have already taken place about the willingness of sites to take part in the full RCT, if funded. We will also start the process of amending relevant approvals and seek a funding review from YCR about continuation to a full trial (see 3.14).

3.12 Intervention and procedure refinement

Based on findings from patient, research and CHMT feedback and fidelity assessment, we will review relevant aspects related to the intervention content and delivery (including staff training, conduct of research procedures and recruitment approach), and discuss potential amendments to the protocol and intervention manual to enhance acceptability with the full team, the ESCAPE PPI and the Steering group. We will use the APEASE criteria [75] and Nominal Group Technique [76] to reach consensus when reviewing intervention components for refinement and inclusion/exclusion and revise the intervention manual and materials accordingly. Due to the straightforwardness of the intervention itself, it is anticipated that changes, if any, will likely concern recruitment and delivery process and trial design, rather than intervention content.

3.13 Funding review

After Phase I, the outcome measures for the feasibility trial will be analysed and discussed with YCR regarding the feasibility of a fully powered RCT during the regular YCR KPI meetings as part of the award monitoring process. Following the feasibility trial, we request a formal “stop/go” point, and further funding for the full RCT will be determined based upon Phase I. A decision as to whether the project should progress to full trial stage will be made based on the following criteria:

a) Recruitment rate of six eligible participants per Trust with two study sites; b) Based on the confidence interval approach, an estimated effect that is larger than zero; c) Consent rate of ~15% of eligible participants, with no more than 30% attrition at follow-up; d) A clear indication of acceptability of the intervention and research process, based on qualitative and quantitative feedback measures collected from participants and research and CHMT staff (including proportion of participants from whom validated biochemical outcome measure (CO) could be successfully collected and successful training of CPN staff

to aid intervention delivery); e) Successful engagement with all co-applicant mental health Trusts for the main trial, with agreement to participate.

At this point, it may be necessary to recommend amendments to the study design/procedure to increase the chances of success of the RCT (see 3.13) and an updated sample size calculation will be conducted.

4. PHASE II – FULL RANDOMISED CONTROLLED TRIAL (MONTHS 13-48)

4.1 Aims

4.1.1 Primary research objective: To test the effectiveness of an e-cigarette starter kit as an adjunct to usual care compared with usual care alone on smoking cessation rates at 6-month follow-up among smokers with mental illness.

4.1.2 Secondary research objectives: To evaluate the impact of the intervention on smoking cessation rates at 1-month follow-up, smoking reduction at both 1-and 6-month follow-up, mental health outcomes and psychosocial measures at 6-month follow-up; to establish cost-effectiveness and assess adherence to and satisfaction with the intervention.

4.2 Design, Randomisation, Treatment groups

We intend to follow a similar approach to the feasibility trial (see Figure 1) for the design (including recruitment method), randomisation, intervention content and delivery in the full RCT, optimised based on findings from Phase I. There will be two main differences: expanded questionnaires to assess all secondary outcomes relevant for a full RCT (see 2.5), and the addition of a follow-up point at 6 months. We judged 6-months abstinence rates to be appropriate, as this is a follow-up period recommended by relevant Cochrane effectiveness reviews [37] and trial guidelines [77]. While the Phase I feasibility trial assessed abstinence at an earlier time point, relapse rates for smoking cessation treatments from one month onwards are relatively stable [78]. Therefore, it can be assumed that if the 1-month abstinence rate observed in the feasibility trial is promising (as assessed by confidence interval approach and Bayes Factor analysis), this will translate into meaningful group differences at 6-month follow-up.

4.3 Participants and procedures

Feasibility-specific data collection aside, participant selection and procedures will be the same as for Phase l, taking into account learning from the feasibility trial.

4.4 Study Sites

In addition to the Trusts involved in the feasibility trial, we will also recruit participants from at least two additional Trusts for the full RCT. Various of the 42 Trusts (including the majority of mental health Trusts in Yorkshire) involved in the SCIMITAR trial have already expressed an interest in taking part. We will also increase the number of sites per Trust from two in the feasibility trial to three (including additional sites within pilot RCT Trusts) to ensure an adequate recruitment rate to complete the full RCT within the proposed

timeframe. In line with the feasibility trial, based on a recruitment rate of six participants per Trust (with two sites), we would seek to recruit around eight participants per month per Trust (with three sites) to achieve a target sample size of 740 participants within the 22 months recruitment period (including a three-month buffer period to account for uncertainty around the exact recruitment rate).

4.5 Measures (see 3.8.1 for baseline measures)

4.5.1 Primary outcome measure

The primary outcome measure is self-reported 7-day point prevalence abstinence, assessed 6 months after study enrolment or target quit date (for those who set a target quit date within one week of enrolment) and verified by exhaled breath CO measurement. Participants will be asked whether they have smoked in the past week and only those responding that they have not had a single puff with a CO reading of less than 10 ppm will be counted as successful quitter. This is a standard outcome measure in tobacco research, recommended for research in populations where the intention to quit on a certain date is not given [79]. Smoking abstinence at 6 months is a strong predictor of long-term effects, thus enabling definitive trials to be conducted efficiently within reasonable resource [80, 81].

4.5.2 Secondary outcome measures

4.5.2.1 Clinical (smoking-related) outcomes: At one month, self-reported and CO-verified smoking abstinence rates, 2-4 weeks from enrolment or target quit date (whichever is later) will be recorded. Continuous abstinence at 6-month follow-up will be defined as not having had more than 5 cigarettes between two weeks after enrolment and follow-up, in line with Russell standards [77]. Unsuccessful quit attempts in the past six months will also be recorded. In line with the feasibility trial, smoking reduction in cigarette consumption by 50% or in CO reading by 30% will be assessed at both 1- and 6-month follow-up.

4.5.2.2 Clinical (mental health-related) outcomes: At 6-month follow-up only, general and mental health functioning will be assessed using measures detailed in 3.8.1.3.

4.5.2.3 Practical (design-related) outcomes: As in Phase I, attrition and, in the intervention group, adherence rate will be assessed at 1-month follow-up. Attrition will also be assessed at 6-months follow-up, in addition to continued use of e-cigarettes in the intervention group and de novo e-cigarettes use in the control group.

4.5.2.4 Psychosocial outcomes: Health-related quality of life will be assessed using EQ-5D-5L [82] and the mental health specific ReQoL [83] at final follow-up. Health and social care service use will be measured using the Client Service Receipt Inventory (CSRI), which has been validated against objective primary care records [84] and is also recommended for usage of hospital and other community health services [85]. Changes from baseline in other health behaviours (see 3.8.1.4) will be determined at 6-month follow-up.

4.5.2.5 Cost effectiveness: To determine short-term cost-effectiveness of the intervention, we will undertake a within-trial incremental cost-effectiveness analysis to assess the value

for money afforded by the intervention over and above the usual care using data collected during the trial. A service use questionnaire piloted in the feasibility workstream will be used to collect resource use at baseline, one and six months and will include both the cost of providing the interventions and the costs of patients' health care utilisation from an NHS perspective as recommended by NICE technology appraisal guide [86]. To assess long-term cost, effectiveness, we will undertake economic modelling (see 4.7).

4.5.2.6 Serious adverse events: Serious adverse events will be monitored, recorded and assessed as per the procedure outlined in Phase I throughout the study.

4.6 Power Calculation

The full trial will be powered to detect a difference between the intervention and control group in our primary outcome: 6-month abstinence rate (see 4.5). Pooling results of the only three RCTs comparing e-cigarettes with placebo e-cigarettes [38, 39, 87] yields an expected effect size of OR 2.01 for 6-months abstinence rates. We consider this estimate to be conservative as most of these trials used older, less effective first-generation e-cigarettes. In fact, a recently published trial comparing an active treatment (NRT) with a modern, third generation e-cigarette in the context of stop smoking services [41] found a superior effect of e-cigarettes on 6-months abstinence rates of OR 1.63. Based on established effect estimates for NRT vs placebo [88], findings from this trial therefore indirectly suggest that compared with placebo/usual care, third generation e-cigarettes (as will be used in this trial) may increase 6-months abstinence rates nearly three-fold (OR 2.85). Using the more conservative effect estimate of OR 2.01, we expect an absolute predicted risk difference of 6.7%, assuming 6-months abstinence rates in the control (standard care) group of 7.7% (based on EAGLES [67] and SCIMITAR-plus [30] trials which were conducted in PWMI) and 14.4% in the intervention (e-cigarette) group. A sample of 740 participants (370 per group) would provide 80% power, with alpha=0.05 in two-tailed analysis to detect this conservative effect. This sample size would also provide 95% power to detect a more likely effect of OR 2.43 (intermediary between the conservative and more optimistic effect), with an absolute predicted risk difference of 9.2% at 6 months (7.7% for control group vs 16.9% for treatment group).

4.7 Proposed analyses

Baseline characteristics will be reported by each arm using descriptive statistics.

4.7.1 Clinical effectiveness

Primary (CO-verified 7-day abstinence rates at 6-month follow-up) and other secondary binary outcomes will be analysed first by Fisher's exact test and then log-binomial regression adjusting for known predictors of cessation [89], comparing the intervention with the control group. Repeated measures analyses (e.g., mixed modelling, generalised linear models) will be used to analyse changes across baseline, 1- and 6-month follow-ups. Analyses of smoking-related outcomes will follow the intention-to-treat principle where those lost to follow-up are treated as smokers. Missing data for other outcomes will be explored to understand if they are missing at random, and appropriate approaches to dealing with missing data (e.g., multiple imputation) will be implemented, if necessary.

Relative risk and 95% confidence intervals will be calculated for all outcomes. As for Phase I, in the event of a non-significant difference between groups on primary and other outcomes, associated Bayes Factors will be calculated using the method of Dienes to differentiate between evidence for no effect from data insensitivity [74]. No subgroup analyses are planned due to limited power to detect effects. All analyses will be carried out by a statistician blinded to intervention allocation. Data will not be unblinded until the end of the study except for consideration of serious adverse events by the data management committee. A full data analysis plan will be developed and published prior to start of data collection on an appropriate trial register.

4.7.2 Cost-effectiveness

To determine short-term cost-effectiveness, we will combine the cost data with health outcomes expressed in quality-adjusted life years (QALYs) measured using EQ-5D-5L to calculate the incremental cost effectiveness ratio (ICER) [90]. We will assess the cost-effectiveness of the intervention by comparing the ICER with the NICE willingness-to-pay (WTP) thresholds range of £20,000-£30,000 per QALY gained [86]. Missing data will be handled by multiple imputation method following Rubin's rules [91]. The imputation will be performed using chained equations by trial arms, assuming any missing data is missing at random. A non-parametric bootstrap re-sampling technique will be used to test the uncertainty of the calculated ICERs (117-120). Based on the results of 5,000 bootstrap replicates, we will plot the probabilities of the intervention being cost-effective over various WTP thresholds on cost-effectiveness acceptability curves [92].

Health economic modelling will be applied to establish long-term cost-effectiveness, beyond the time horizon of the project. The health economists involved in this application have pioneered the use of decision models to judge longer term health impact and cost effectiveness in this area [93, 94]. Based on a decision analytical model developed at the University of York, we will construct a Markov model to make long-term projections of both health gain and health care costs associated with the two trial interventions [93, 94]. The long-term costs are calculated based on the healthcare resources used for treating smoking-related diseases for smokers and quitters, by age and gender [95, 96]. We will employ the cost-of-illness methods introduced by the WHO Economics of Tobacco Toolkit [97] using appropriate reference data [98] and incorporating relapse for quitters [99-101]. The results of the model will provide information with regard to long-term value for money and can be compared to the NICE decision-making threshold. The model will incorporate uncertainty using probabilistic sensitivity analysis and we will demonstrate the probability that ESCAPE would be a cost-effective use of health care resources.

We do not anticipate involving a dedicated CTU in this research project, given extensive experience of the administration and day-to-day running of large-scale smoking cessation RCTs at our Department at UCL without an CTU (e.g. [102, 103]) and the involvement of an experienced statistician (EB) in this project. We will, however, avail of ad-hoc CTU services provided at UCL for some aspects of the trial, including randomisation, case report form (CRF) checks and database development.

4.8 Phase II Milestones

Phase II will begin on 1st September 2022 for the remaining months 13-48. As the necessary approval processes (e.g. NHS Research Ethics Committee) and discussions with additional sites will have been initiated in the latter months of the previous phase, alongside the analysis of the feasibility trial data and YCR funding review, we anticipate a 4-month study set-up period for the additional sites and adaption of intervention processes (if required) and to provide intervention training to new sites and a refresher to existing sites. In parallel, we will focus on preparing and writing up findings from the feasibility trial for submission to an international conference and academic journal (see 2.10). Recruitment will begin in month 17 and last for a 22-month period (until month 38). A 19-month recruitment period will require approximately 39 participants to be consented per month (8 participants per Trust) to reach the 740-participant target, allowing an additional three month buffer period to complete recruitment by the end of month 38. Follow-ups will start 1 and 6 months after recruitment and finish in months 39 and 44, respectively. This leaves a further 4 months for analysis and writing the reports for YCR and publication (months 45-48).

5. DISSEMINATION

Results from the feasibility and full RCT will be shared with study participants via email or text message, which will include a link to blog posts regarding study results. PH and SH, together with lay representatives of the steering committee will assist in ensuring that blog posts and other relevant approaches to dissemination are understandable to a lay audience and will also assist with dissemination (e.g. via social media). If they wish to, participants can also assist with dissemination, and we will work together to prepare social media/blog posts that they can share. We will also work with local press (e.g. Yorkshire Post, Sheffield Star, Doncaster Free Press newspapers) to communicate study results to the local population. In addition, we will approach media offices of Universities and Trusts involved in the study and the Yorkshire and Humber CRN to disseminate study results internally. At national level, we aim to publicise study results through our partners (ASH, NSCST and Equally Well) as well as our contacts within Public Health England and NICE. At international level, findings from both the feasibility and full RCT will be presented at relevant conferences (Society for Research of Nicotine and Tobacco; Society of Behavioral Medicine, Royal College of Psychiatrists etc) and publication of study protocol, and results from both trials in high impact, relevant journal (e.g. JAMA Psychiatry, Lancet Psychiatry). Further, we will plan a media briefing with the Science and Media Centre with whom we have good working relationship.

6. DATA STORAGE AND DATA PROTECTION

Data will be stored in accordance with the Data Protection Act 1998. All data will be collected electronically and stored on a password protected server at UCL using REDCap (a secure web-based data storage system) within their Data Safe Haven system. Participants' identification numbers will be used to uniquely identify patients on the online electronic case report form. All other essential documents, including source documents, will be retained for a minimum period of 10 years after study completion.

7. INDEMNITY

The sponsor of the trial is the University of York.

University of York holds insurance against claims from participants arising for negligent design and trial management for injury caused by their participation in this clinical trial. The policy will be reviewed annually by the University of York, to cover the necessary 4 years of the study. Participants may be able to claim compensation if they can prove that the University of York has been negligent. However, as this clinical trial is being carried out in UK NHS trusts, the trusts continue to have a duty of care to the participant of the trial. University of York does not accept liability for any breach of conduct within the Trusts, or any negligence on the part of Trust employees.

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