Study Protocol

1. TITLE PAGE

Full Title	Helping people cope with temptations to smoke to reduce relapse: A factorial randomised controlled trial
Short Title/Acronym	RP Trial
Sponsor	Queen Mary University of London (QMUL) Contact person of the above sponsor organisations is: Mays Jawad Head of Research Resources Joint Research Management Office 5 Walden Street London E1 2EF Phone: 020 7882 7260 Email: sponsorsrep@bartshealth.nhs.uk
REC Reference/IRAS number	16/LO/1771
Chief Investigator	Professor Peter Hajek, Health and lifestyle Research Unit, Wolfson Institute of Preventive Medicine, Queen Mary University of London
Sites	1. Queen Mary University of London Health and Lifestyle Research Unit 2 Stayner's Road London E1 4AH 2. Cancer Council Victoria 615 St Kilda Road Melbourne Victoria 3004 Australia **NB. This site has a separate sponsor and protocol, which will be reviewed separately by an Australian Ethics committee**

Contents Page

2. GLOSSARY of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTIMP	Clinical Trial of a Medicinal Product
DMEC	Data Monitoring and Ethics Committee
EC	Electronic cigarette
EMA	Ecological Momentary Assessment
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
JRMO	Joint Research Management Office
NHS REC	National Health Service Research Ethics Committee
NHS R&D	National Health Service Research & Development
NRT	Nicotine Replacement Treatment
Participant	An individual who takes part in a clinical trial
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QD	Quit Date
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RP	Relapse Prevention
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SR	Smoking Replacement

SSA	Site Specific Assessment
SSS	Stop Smoking Service
S3P	Structured Planning and Prompting Protocol
TMG	Trial Management Group
TSC	Trial Steering Committee
UC	Usual Care

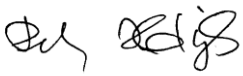
3. SIGNATURE PAGE

Chief Investigator Agreement

The clinical study as detailed within this research protocol (Version 4.1, 08 August 2018,), 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.

Chief Investigator Name: Professor Peter Hajek

Chief Investigator Site: QMUL



Signature and Date: 09.02.2017

NB. Professor Hajek is also the Principal Investigator

Statistician Agreement Page (as applicable)

The clinical study as detailed within this research protocol (Version 4.1, 08 August 2018), or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements.

Statistician Name: Professor Sarah Lewis

Signature and Date: 09.02.2017

4. SUMMARY/SYNOPSIS

Short Title	RP Trial
Methodology	Factorial randomised controlled trial
Research Sites	1. Queen Mary University of London Health and Lifestyle Research Unit 2 Stayner's Road London E1 4AH 2. Cancer Council Victoria 615 St Kilda Road Melbourne Victoria 3004 Australia **NB: this site has a separate sponsor and protocol, which will be reviewed separately by an Australian ethics committee**
Objectives /Aims	To determine if providing additional strategy designed to cope with temptations to smoke (behavioural support and/or access to smoking replacement [SR]) reduces relapse rates in short-term ex-smokers over a 12 months follow-up period.
Number of Participants/ Patients	Main study: 1400 participants (700 at each site – Australia and UK) Qualitative sub study: subset of 160 of the main study participants (80 at each site) Ecological Momentary Assessment sub study: subset of 200 of the main study participants (100 at each site)
Main Inclusion Criteria	- Users of the SSS or Stoptober support in the UK who are abstinent in the last 2 weeks of treatment (treatment period is typically 4 weeks post quit date, QD) - Willing to use a smoking replacement product or online behavioural support tool if allocated to use - Aged 18 years and older - Own a mobile phone - Has Internet access - Able to read/write/understand English
Statistical Methodology and Analysis (if applicable)	Statistical methods will be described in an analysis plan to be agreed and finalised prior to analysis. In summary, we will present baseline characteristics for the four treatment groups according to the main baseline covariate measures defined below. Analysis of the primary outcome will use logistic regression to compare the odds of relapse between treatments, with adjustment for country and SSS/Quitline service as a stratification factor. Reduction in cigarette consumption will be analysed by linear regression. We will conduct a within trial incremental cost-effectiveness analysis to estimate the incremental cost per person quitting smoking based on quits at follow up and also a longer-term projection of health gains and long-term cost savings. Qualitative data will be analysed using the 'Framework' method. Real-time data collected using the electronic diaries will be analysed using mixed models.
Proposed Start Date	01.04.2016 (study start date, including study set up and obtaining approvals) 01.09.2016 (proposed recruitment start date)
Proposed End Date	30.09.2019 (study end date, including write up)
Study Duration	33 months from start of data collection.

5. INTRODUCTION

Background

Around 70% of smokers who quit in the short-term return to smoking within a year. The UK Government invests some £84.3 million annually to fund Stop Smoking Services (SSS), not including the cost of smoking cessation medicines, and there are other investments in encouraging smokers to stop smoking via media and primary care. The initial 4-week quit rates in smokers who engage in treatment are around 50%, but in the longer term, the ubiquitous relapse substantially reduces the impact of these initiatives [1]. As the health benefits of stopping smoking are primarily realised with long-term abstinence, relapse reduces the public health benefit of investment in smoking cessation interventions and remains the main unresolved issue of smoking cessation efforts. Preventing relapse is currently the number one priority within the field and new approaches are urgently needed.

Clinical data

A comprehensive research programme into the real-life causes and time-course of relapse by means of Ecological Momentary Assessment (EMA) has concluded that relapse situations are triggered by a host of different mechanisms and are difficult to predict and counteract [2].

Another important finding was that 90% of single lapses (i.e. smoking one cigarette or just taking a single puff) lead to full blown relapse [3]. It appears that even after a lengthy period of abstinence, a lapse generates a priming effect on the dopamine reward pathways [4] which leads to further smoking.

There are three main trajectories to long-term abstinence that interventions can influence. First, they can focus on preventing a lapse from occurring. Secondly they can act to prevent a lapse progressing to relapse, and thirdly they can focus on people who relapse encouraging them to reengage with treatment again, within days of relapse [5].

Up to now, only two behavioural relapse prevention (RP) strategies have been formally evaluated: a ‘skills-based’ approach which focuses on teaching clients to identify relapse situations and put in place coping strategies [6]; and extending the initial treatment with maintenance sessions to provide on-going support.

A systematic review of this literature for the Cochrane Collaboration [7] identified 54 studies relevant to relapse prevention. Disappointingly, despite good intuitive validity of these interventions, no single study or a combination of studies showed a significant benefit. Other systematic reviews have arrived at the same conclusions [8]. Clients may not learn the cognitive-behavioural skills or may not practice them, or the skills may not be helpful [9].

The Cochrane Review also identified eight studies that examined the extended use of stop smoking pharmacotherapy [7]. Extended use of varenicline (6 months versus the standard 3 months; 1 study) was associated with a small increase in 1-year abstinence rates (RR = 1.18; 95% CI: 1.03-1.36), but no benefit was found for extended use of either bupropion or nicotine replacement therapy (NRT). Most

successful quitters see little reason to continue using currently licensed smoking cessation medicines, resulting in low uptake [10, 11] and long-term use of these medicines also has serious financial implications. Our strategy overcomes these problems as it is testing a behavioural programme that will have no long-term costs, and the smoking replacement (SR) intervention is based on participants being prepared to continue use at their own cost, something we believe is viable.

New vaporised nicotine (VN) products, such as e-cigarettes (EC), have become popular among smokers [12, 13] and preliminary data suggest that they may be helpful for smoking cessation. EC may be more effective than current smoking cessation medicines for preventing relapse for several reasons including: (i) they are more psychologically attractive to smokers [14, 15] and therefore more likely to be used more often and for longer; and (ii) they replace more of the desired effects of smoking. VN, and EC in particular, are cheaper (from the NHS perspective) than standard medicines (e.g. NRT, varenicline) as they are likely to be purchased by the user. There are few other smoking cessation treatment improvements on the horizon and VN are the most promising current development awaiting objective scrutiny. SSS and policy makers are asking for data that will guide their decision making [16] and although the tobacco control community is divided on their opinions of EC, there is agreement that more data are urgently needed on the role these and other alternative nicotine devices may have to play.

Regarding behavioural support, there is evidence that extended support during the initial treatment period improves smoking cessation outcomes and several trials have looked at using this approach for preventing relapse [7]. However, the support relied on smokers taking the initiative to telephone the service when they felt in danger of lapsing or following a lapse. Not surprisingly, very few clients used the offer. Successful quitters do not see the necessity to have regular contact when they are not smoking, and once lapsed to smoking believe that there is no benefit in making contact. The intervention we will be using shows promise of sustaining its effects beyond the period of active training and support.

Modern information technology, in particular web-based resources and text messaging, offers a new and more convenient way of maintaining contact with clients to provide on-going support. Recent data show that an online Structured Planning and Prompting Protocol (S3P) reduced relapse rates between 1-24 weeks from 71% to 61% [17]. S3P is designed to focus planning on strategies to deal with temptations to smoke. The core element is using a method of “If in a particular situation, then do some specific set of actions to prevent relapse”. This form of self-statement has been shown in experimental work to improve the cuing of the desired action in the context of the situation occurring where it is likely to be needed [18] . This approach can be delivered online and can be enhanced by mobile phone text messages. Digital technology promises a new approach to extending supportive contact. Texting interventions are inexpensive and can be easily disseminated on a large scale. We have piloted the use of ongoing text-based contact to prevent relapse in 202 SSS clients, who were abstinent 4-weeks after their quit date [11]. Clients received 17 personalised messages, 9 that were interactive, which were sent weekly for 12 weeks and fortnightly for 6 months. Unlike invitations to attend sessions or call their advisors, the texting intervention was well received by recent ex-smokers (70% gave an overall score for helpfulness of the messages of 4 or 5 on a 5-point scale) and the retention rates were much better than with face-to-face or reactive telephone-based approaches.

The proposed trial would be the first randomised study of these interventions for relapse prevention, and thus will generate new knowledge. The intervention itself would build directly on previous UK and Australian work while the trial would use methods validated extensively in previous research.

Rationale and Risks/Benefits

Smoking is the largest preventable cause of illness and premature death and costs the NHS around £5.2 billion per year. In Australia, the investment in tobacco control is $71 million.

Both the UK and Australia have strong tobacco control policies and continue to sustain a slow decline in smoking prevalence. Most smokers are trying to quit and although many achieve short-term abstinence they have subsequently relapsed [19].

The UK Government alone invests some £84.3 million annually to fund SSS which has been shown to be effective and cost-effective [20]. Over 5 million smokers have set a quit date through the SSS since their inception in 2000, with over 2.5 million quitters at 4 weeks after their quit date [21]. However 70% will relapse within a year [1] which reduces the impact of the investment. Preventing longer-term relapse would thus greatly increase the longer-term impact of cessation efforts.

EC and NRT use does not involve tobacco combustion, which is the primary source of the many thousands of dangerous chemicals to which smokers of conventional cigarettes are exposed. The safety profile of NRT is well established, and so far EC appear to have an acceptable safety profile also [14, 22] with no clinically significant levels of any harmful chemicals having been detected in vapour of EC [23]. In clinical trials conducted to date, EC have had a similar (favourable) adverse event profile to NRT [15]. There is little doubt that EC are substantially safer than conventional cigarettes, and they have the potential benefit of reducing urges to smoke and relapse rates.

This study aims to examine if two RP interventions - behavioural (access to an online S3P programme), or smoking replacement (access to EC/NRT) - either individually and/or synergistically, can reduce rates of relapse between 4 weeks and 12 months post quit date (QD) in those that receive the RP interventions compared to usual care.

6. TRIAL OBJECTIVES

Primary Objective

To determine if providing additional strategies designed to cope with temptations to smoke (behavioural support and/or access to smoking replacement [SR] products) when provided following the successful completion of a smoking cessation programme (i.e. at around 4 weeks post quit) or Stoptober support reduce relapse rates at 12 months post quit date.

Secondary Objectives

To determine:

1. Are the outcomes of the trial affected by alternative definitions of successful quitting and/or assumptions made about the status of missing cases?
2. If the strategies work, is this by reducing slip-ups and/or by enhancing recovery from slips, including short term relapse, or by some combination of the two? (EMA/qualitative sub studies complementing reports at follow-ups)
3. What, if any, sustained reductions in cigarette consumption occur (particularly reductions to non-daily use), among treatment failures and does this relate to any coping strategy?
4. What is the cost-effectiveness of any effective strategies, and does this differ between countries?
5. Do the strategies have different effects on people from different socioeconomic and ethnic groups, of different gender, with different prior smoking habits, and those who stopped smoking using different forms of medication?
6. How feasible and acceptable are the strategies to participants, and what are the barriers and facilitators to sustained cessation during the trial period? How are the relapse prevention strategies used, and are patterns of use related to cessation outcomes?
7. What are the rates of negative aspects reported in people who use a smoking replacement product compared to those who do not and does this vary by type of product used?

Primary Outcome

Sustained abstinence between 1 and 12 months post quit date, with no reported relapse (7 or more days of continuous smoking and no smoking at all in the last month, biologically validated). The primary analysis will be intention to treat, including all those randomised and those with missing outcome data presumed to have relapsed.

Secondary Outcome

1. Sustained abstinence using different criteria to the primary outcome and different assumptions about missing cases
2. Point prevalence and shorter-term period prevalence outcomes
3. Sustained reduction in cigarette consumption
4. Evaluations of likely mechanisms of effect in particular focusing on these strategies that were encouraged and participant perceptions of effect (e.g. participant ratings), including use of EMA/qualitative sub studies
5. Dose response effects. Testing whether the dose of the interventions, or extent of compliance, is associated with relapse
6. Cost-effectiveness of the different strategies
7. Effects of intervention components (e.g. on relapse rates, participant ratings etc.) by country and on people from different socioeconomic and ethnic groups, of different gender, with different prior smoking habits, and those who stopped smoking using different forms of medication

7. METHODOLOGY

Inclusion Criteria

- Users of the SSS or Stoptober support in the UK who are abstinent in the last 2 weeks of treatment (treatment period is typically 4 weeks post quit date, QD) and are still abstinent at point of recruitment
- Willing to use a smoking replacement product or online behavioural support tool if allocated to use
- Aged 18 years and older
- Own a mobile phone
- Has Internet access
- Able to read/write/understand English

Exclusion Criteria

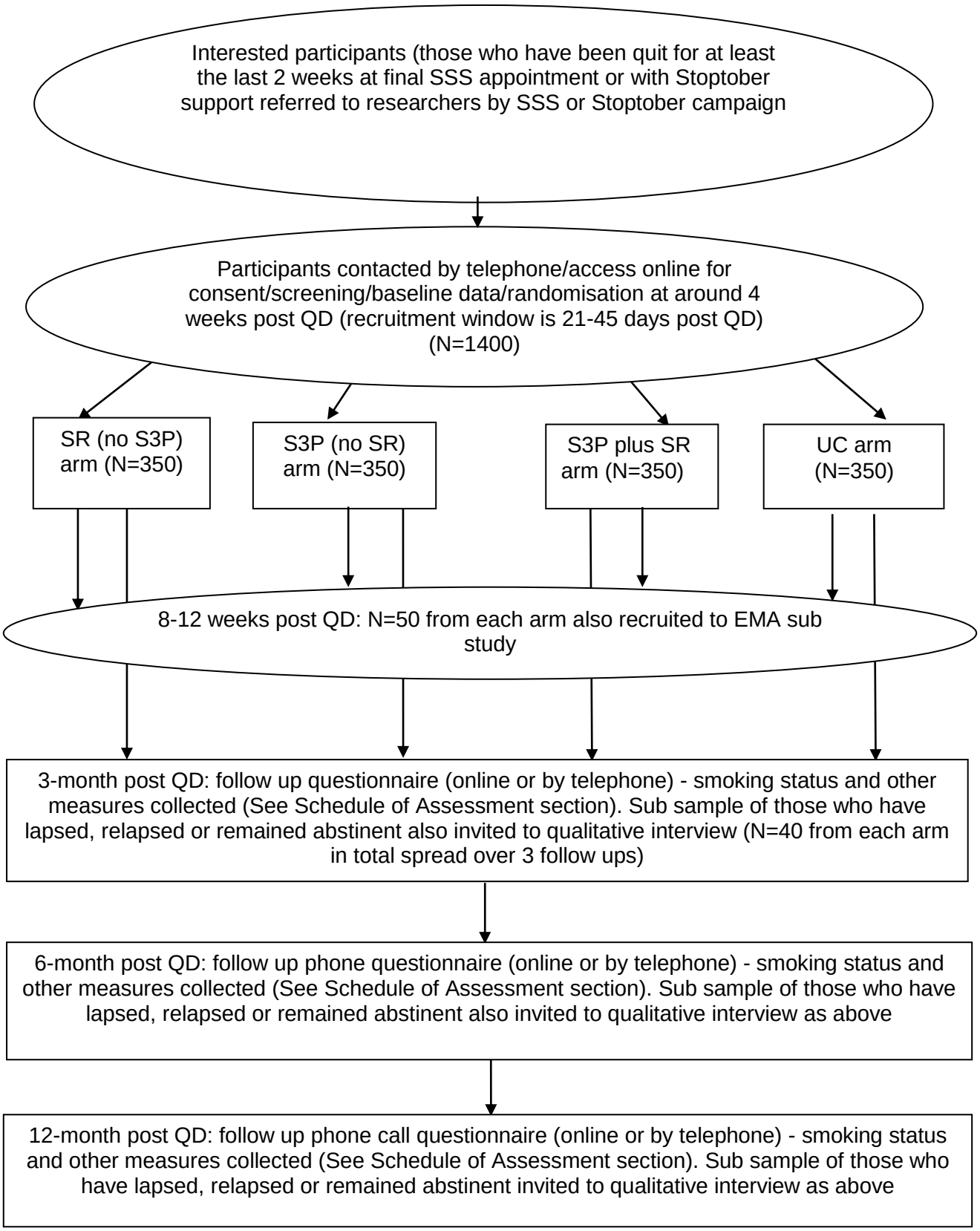
- Enrolled in other smoking cessation/relapse prevention research
- Currently using EC/oral NRT and planning to use for longer than 3 months

Study Design

This is a factorial randomised controlled trial with two comparisons added to usual care (UC; UC is generally 8-12 weeks of pharmacotherapy (e.g. varenicline or NRT), plus standard counselling provided from the commencement of the quit attempt or less intensive Stoptober campaign support), augmented by a series of text messages available in all conditions. Participants will be individually randomised to one of four arms: UC (Usual Care), SR (Smoking Replacement), S3P (Structured Planning and Prompting Protocol), or SR plus S3P).

Study Scheme Diagram

The study scheme overleaf outlines the flow of participants through the trial and key time points. Full details about the interventions is given in the Schedule of Intervention section.


Interested participants (those who have been quit for at least the last 2 weeks at final SSS appointment or with Stoptober support referred to researchers by SSS or Stoptober campaign
Participants contacted by telephone/access online for consent/screening/baseline data/randomisation at around 4 weeks post QD (recruitment window is 21-45 days post QD) (N=1400)
SR (no S3P) arm (N=350)
S3P (no SR) arm (N=350)
S3P plus SR arm (N=350)
UC arm (N=350)
8-12 weeks post QD: N=50 from each arm also recruited to EMA sub study
3-month post QD: follow up questionnaire (online or by telephone) - smoking status and other measures collected (See Schedule of Assessment section). Sub sample of those who have lapsed, relapsed or remained abstinent also invited to qualitative interview (N=40 from each arm in total spread over 3 follow ups)
6-month post QD: follow up phone questionnaire (online or by telephone) - smoking status and other measures collected (See Schedule of Assessment section). Sub sample of those who have lapsed, relapsed or remained abstinent also invited to qualitative interview as above
12-month post QD: follow up phone call questionnaire (online or by telephone) - smoking status and other measures collected (See Schedule of Assessment section). Sub sample of those who have lapsed, relapsed or remained abstinent invited to qualitative interview as above

8. STUDY PROCEDURES

Informed Consent Procedures, Screening, Enrollment

In the UK, participants will be recruited from local SSS where they have enrolled and received UC and are quit for at least 2 weeks on their last scheduled call/visit (typically this is around 4 weeks quit) or from Stoptober support. UC generally includes base medication (e.g. nicotine patch, varenicline or bupropion), plus a course of counselling support typically up to 4 weeks post QD. Participants who have used a base medication in UC will continue to use their UC medication until end of UC treatment protocols (around 8-12 weeks post QD, unless they choose to stop base medication early) regardless of which study arm they are allocated to.

The following SSS have provisionally agreed to refer potential participants: Tower Hamlets, Quit 51, Solutions 4 Health and Torbay and Southern Devon. Additional SSS involvement will be sought during the study if required.

Service users or smokers using Stoptober support who have been quit for at least 2 weeks at around 4 weeks post-QD will be informed of the study by the SSS or Stoptober campaign.

If interested/eligible participants will be given written information by the SSS or Stoptober support campaign and referred to the research team.

All those interested will be contacted by GCP trained researchers as soon as possible; those who are quit but not yet in the recruitment window (which is 21-45 days post-QD) will be asked if interested by the advisors at the SSS and Stoptober support, but will not be contacted by the research team until they enter the recruitment window. Obviously, those relapsing in the interim will not be eligible. Participants will be given sufficient time to read and consider the information contained in the participant information sheet and ask any questions before making a decision about whether to participate. It is anticipated that the majority of potential participants will have at least 2 days to decide.

Participants will be screened for eligibility either online, or over the telephone (depending on the participant's preference) by GCP trained members of staff who are delegated to do so on the delegation log. Depending on the screening method, participants will either give verbal informed consent or electronic informed consent. Those consented will undertake a baseline survey collecting a range of data to describe socio-demographic, smoking characteristics, quitting experiences and other measures before being immediately randomised into 4 groups (see Randomisation section below for full details) with initiation of the protocol for their allocated treatment condition.

Randomisation Procedures

Participants will be randomised (stratified by country [and service within the UK in the study analysis] in permuted blocks of random size) to one of four study arms described in the Schedule of Intervention below. Randomisation will be done automatically via R code with the results imported into the web based program

(Quest Engage) that directs the baseline study questionnaire, and will occur after all key baseline information has been collected. Apart from the differential offer of help, the randomisation will also tailor subsequent questions relevant to those in each condition.

Schedule of intervention
Common to all interventions is provision of text messages provided for up to 6 months post quit, which provide reinforcers of milestones, general motivational messages and some general hints. NB. This is a non-interactive, untailored version of the text messages provided in the S3P condition.

The two key interventions are:

1. **Smoking Replacement (SR)**

After being given information about the available SR products, participants will be asked to choose one to use as a coping strategy if they find themselves at risk of relapse. Up to three NRT and EC options will be available to choose from. See section 14 Products, devices, techniques and tools for further details.

The selected product will be couriered to the participant so that they have it at hand if needed. Participants will be proactively offered further supply, via an email sent by the study team, at 8-weeks post-QD. After this, participants who need further supplies will be encouraged to buy/access any further supply themselves.

How to use the product as a strategy for coping with present or anticipated temptations to smoke will be explained to participants, and a leaflet which contains this information will be provided. Participants will receive a follow-up call targeted within a week of randomisation (by which point they will have received their chosen product) to talk about how to use the product effectively.

2. **The S3P intervention (Structured Planning and Prompting Protocol)**

Participants will be invited to complete a web-based assessment that generates a 3-4 page letter of personalised advice, a list of priority activities (e.g. remind yourself of the experienced benefits of having quit; practice replacement strategies; develop alternative activities to do while taking breaks; develop a recovery plan for if you do slip-up and smoke etc.) with the prioritisation based on assessment responses. In addition, it provides) a structured tool for generating if-then statements for strategies for avoiding smoking when the urge to smoke occurs.

The tool will contain separate strategies for those using and not using SR products, and will also provide more general advice about countering more stable residual beliefs about the value of smoking, and suggestions for monitoring the ongoing benefits of having quit and taking appropriate rewards for reaching milestones. The web-based intervention (which can be used as often as the person desires – advice changes with changing circumstances) will be augmented by a series of text messages provided for up to 5 months (i.e. to 6 months post-QD) which will reinforce the need to use if-then statements, provide motivational messages, plus some more generic advice. Both components of the intervention have interactive elements, with the text messaging program being able to respond to a variety of requests for additional help from the user. Because

of concerns about the motivation to use additional help at this time in the quit attempt, we will optimise the intervention for use on mobile phones. The frequency of base-text messages will be tailored to the needs of the participant with a core number of up to 72 for those reporting the most difficulties. NB: Any participant-requested additional messages will be on top of these frequencies.

All participants will receive a follow-up call targeted within 1 week of randomisation to talk about how to use the intervention effectively.

This results in four experimental conditions. NB. All participants receive all elements of UC (including using UC medication provided by the SSS until the end of UC treatment protocols if they wish) except where explicitly stated.

1. **UC arm (control group, receives neither intervention):** If used as part of UC, this group will be encouraged to continue use of base medication (e.g. varenicline or NRT) until the end of the recommended period of use.

   They will be given a brief message warning that relapse is common even after succeeding for 1 month and will be encouraged to persist, and offered a version of the text messaging program without the specific strategies focused on in the S3P intervention. They will not be provided with any SR products (although they may be using them as part of their continued UC at the SSS).

2. **Only SR:** This group will be offered a SR product. Participants will choose one SR product from up to three NRT and EC options to use as a coping strategy if at risk of relapse. See section 14 Products, devices, techniques and tools for further details.

3. **S3P / No SR arm:** Participants will receive an initial personalised, tailored plan, and access to the Structured Planning and Prompting Protocol (S3P) designed to focus planning on strategies to deal with temptations to smoke, reinforced with additional text messages that will remind them to rehearse these self-statements, replacing some of the more general messages used in the UC condition. These resources will be available to them on the internet for future use, with prompts to use when recommended (around the time of stopping base medication or when having additional problems.

4. **S3P plus SR arm:** Participants will receive both interventions, with S3P modified to include integrated references to SR as a relapse prevention strategy.

Follow-up

Participants will complete online questionnaires at 3, 6 and 12 months post-QD (approximately 2, 5 and 11 months post-recruitment) for smoking status and other measures (see Schedule of Assessment section). Participants will have the option of being contacted by telephone to complete the questionnaires if they prefer. Participants will receive £10 for completing the questionnaires at 3 and 6 months and £20 at 12 months. Those reporting abstinence at 12 months will be sent a saliva swab sample kit, along with instructions on how to provide the sample and a stamp

addressed envelope to return it in. Participants will receive £20 for returning their saliva sample.

Although the research team will have telephone contact with some participants at 3, 6 and 12 months to assess outcomes, no counselling will be provided; the researchers involved will not have such expertise and will tell participants this if they seek advice. If participants ask about the utility of strategies, including continued use of UC base medication, they will be told “this can help” for any suggestion where there is evidence of benefit, and “there is no evidence that this can help” for any without an evidence base. Issues raised will be documented and we will follow up specifically to see if any potentially effective strategies were used.

NB. Participants who do not want to use a nicotine based product will not be randomised in to the study, but will be offered access to the S3P program, and will be followed up passively only (i.e. they will receive email reminders to complete the follow up questionnaires online, but will not be actively followed up by the study team).

Qualitative and EMA sub studies

At 3, 6 and 12 months post QD a sub sample of participants who have relapsed, lapsed, or remained abstinent will be invited to take part in a qualitative interview (N=160 in total, split equally between the 2 countries and 4 arms). See Qualitative Sub Study below for full details.

At 8-12 weeks post QD a subset of 50 participants from each arm will be recruited to take part in three weeks of Ecological Momentary Assessment (EMA) monitoring, which includes detailed monitoring of the use and relationship to cravings and slips of the two interventions using a handheld electronic diary [24]. See EMA Sub Study below for full details.

1. Qualitative sub study

The main aim of the qualitative research is to investigate barriers to sustained cessation at 12 months. However, interviews will be staggered over the course of the year in order to capture information from relapsers shortly after they have relapsed.

All participants will be provided with written information about the qualitative sub study when they are informed about the main study. During the 3, 6 and 12 month follow up calls we will identify people who have 1) relapsed, 2) lapsed, or 3) abstained and invite them to participate in an interview. Those who agree to take part, will give either verbal informed consent or online consent, and a convenient time to conduct the interview with the researcher will be agreed. A GCP trained researcher will conduct the semi-structured telephone interview at the agreed time. The interviews will explore triggers to returning to smoking, and where appropriate, the circumstances of relapse and what might have prevented this. No counselling will be provided during the interviews; the researchers involved will not have such expertise and will tell participants this if they seek advice.

Interviews will be tape recorded and transcribed.

We aim to recruit 20 interviewees from each arm of the intervention in each country (total 80 per country, 160 overall) using quota sampling to try and obtain a cross section of participants who have lapsed/relapsed/maintained abstinence. Each participant will only be interviewed once. All interviews will include feedback about the interventions, usage and perceived helpfulness. We will also have access to the EMA data, where appropriate, to help inform some interviews.

Participants in the qualitative sub study will receive £20 per completed interview.

2. EMA sub study

To further examine the use of the interventions and their effects, we will include a sub study that utilises EMA. A subset of study participants (n=200; equally split across the four study arms and two countries) will be recruited to take part in three weeks of detailed monitoring using a handheld electronic diary [24]. These devices will be loaded with custom EMA data collection software. As the objective is to monitor the use and effectiveness of the two study interventions, detailed monitoring will take place immediately following the cessation of base medication, where applicable (for most participants this will occur approximately 4-8 weeks after randomisation, 8-12 weeks post-QD). During the three weeks of monitoring participants will complete multiple daily assessments. They will be asked to log every time they use a SR product (if using), any lapses that may occur, and to respond to randomly scheduled prompts (4-5 per day); additionally, they will be asked to complete a daily morning and evening report.

The EMA device will be used to administer multiple types of questions across various assessments. The assessments include: baseline data, logging of cravings and/or slip-up cigarettes, detailed questions about a subsample of these situations, and daily reports of mood and overall coping. The detailed questions include an assessment of the participant's current state (e.g. mood, withdrawal severity, craving etc.) as well as contextual and situational details (e.g. where the participant is, who they are with, what they are doing etc.), the trigger of the event (e.g. bad mood, smoking cues etc.) and the use of any coping strategies during the event. To avoid over-burdening participants with assessments, only a sub-set of reported events will be sampled for full assessment; a strategy that we have successfully implemented in previous studies [25]. Items in the proposed EMA assessments have been used and validated in previous EMA studies, are reported in detail in resulting publications [26-28] and are in use in studies currently being run by the Australian study team. The device will log the time and date of events and store this data for later download and analysis.

All participants will be provided with written information about the EMA sub study when they are informed about the main study. During the one week post randomisation call for the main study, participants will be informed about the EMA study and asked if they would be interested in taking part, if selected to. At 4-8 weeks post randomisation, a selection of those who expressed an interest will be invited to take part in the EMA sub study. They will be given further information about the sub study and the opportunity to ask any questions they may have. Those who agree to take part will give either verbal informed consent or online consent depending on their preference. Consented participants will be trained on EMA procedures and on assessment content before field monitoring commences. Participants will be contacted (either by telephone or via email) during the first three days of EMA

monitoring to ensure they understand and are following procedures and they will receive further EMA training (if necessary). Participants may be contacted at additional times during the EMA monitoring to ensure compliance with study procedures. Participants will be sent a reminder e-mail and/or text message 24 hours before a scheduled phone call. At the end of each call, the next one will be scheduled. At the end of EMA monitoring the devices will be retrieved and re-used with subsequent participants. Participants taking part in the EMA sub study will receive £60 for fully completing the assessments.

Measures

Baseline:

- Demographic details, smoking measures (e.g. heaviness of smoking index referenced to when they were smoking [29] information regarding previous quit attempts) and medical history (e.g. screening for depression, measures of perceived stress and affect)
- Information regarding the current quit attempt (including type of support/medicines used), frequency and strength of cravings, extent of slip-ups if any, plans on how long to continue use of base medication, self-efficacy for maintenance, perceived challenges, number of smokers in social network
- Quality of life as measured by the European Quality of Life-5 Dimensions (EQ5D)[30].
- Health Service Use Questionnaire

All follow ups:

- Self-reported smoking status and cigarette consumption
- Detailed lapse/relapse report for those relapsing (e.g. no. of lapses, when, where, reasons, how many cigarettes at first lapse, how soon after first cigarette was full relapse)
- Strategies used to prevent relapse
- Cravings to smoke
- Participants who stop using SR/S3P/UC will be asked their reasons for doing so (if using at previous survey).
- Use of any, including non-allocated, smoking cessation/relapse prevention treatments
- Detailed use of SR/S3P/UC and ratings of the interventions, including helpfulness and any negative aspects (3 and 12 month follow up only).
- Consumption of alcohol (binge drinking), including changes in consumption [31]).

12 month follow up additions:

- Saliva sample collection for those abstinent at 12 months. Cut off for abstinence is cotinine < 15 ng/ml [32]for those not reporting using any nicotine product and anabasine < 1 ng/ml [33] for those reporting other forms of nicotine use
- European Quality of Life-5 Dimensions (EQ5D) questionnaire
- Health Service Use Questionnaire

Routinely collected data:

- Use of the S3P will be collected by capturing data on the number of log-ins and the time spent in the programme, including number of assessments and time received text messages.

Procedure for Collecting Data

Non-identifiable participant data for all study arms will be collected using the servers on which the S3P intervention is run (for baseline data) and REDCap (for follow up data). We intend to duplicate the database and intervention back-end components to ensure that any participant identifying data is stored within the country it is collected. This data (i.e. name and contact details for the purposes of contacting participants and generating reminder texts) will be stored separately to the study data, with the exception of mobile telephone numbers and email addresses, which will be stored alongside study data (in their respective countries) for the purposes of sending the intervention texts and emails (the texts and emails are tailored based on responses to some study questions, and therefore these responses need to be linked to the mobile numbers). When data from the two countries is combined for analysis, this will occur only in de-identified form.

This data management application will adhere to the standard operating procedures (SOPs) of the Barts Clinical Trials Unit (CTU) and they will provide general oversight for the UK component of this study. The servers in both countries will be kept in a secure, locked room with restricted access and the databases will be password protected.

Subject withdrawal

Participants will be able to discontinue using their allocated intervention at any time. This will not affect their usual medical care. Participants that discontinue using their allocated intervention will be followed up at 3, 6 and 12 months post QD unless they do not wish to be. Participants who do not wish to be followed up would be withdrawn from the study.

Unless withdrawn participants request otherwise, data collected up to the point of their withdrawal will be used in the study analysis. Any participants who die during the study will not be included in the analysis, and another participant will not be recruited in their place, in accordance with the Russell Standard [32]. Any participants who die during the study will be included in serious adverse event reporting. We do not foresee any other reasons to withdraw participants.

Schedule of Assessment

Study measures and procedures		Time Point			
Measures/Procedures	~4-weeks post QD	~8-weeks post QD	~3-months post QD	~6-months post QD	~12-months post QD
Demographics	X				
Smoking history	X				
Detail on current quit attempt	X				
Randomisation and post randomisation phone call	X				
Smoking status/cigarette consumption	X		X	X	X
Slip-ups and cravings	X		X	X	X
Collection of saliva					X
Use of help, pharmacological or professional, including web-based interventions	X		X	X	X
Use and feedback of S3P (allocated cases only)			X		X
Use of SR products (allocated cases only)	X		X	X	X
Ratings of interventions (including helpfulness and negative aspects)			X	X	X
EMA (sub study participants only)		X	X		
Qualitative interviews (sub study participants only)			X	X	X
Health Service Use Questionnaire	X				X
Quality of life measures	X				X

End of Study Definition

The study would be completed and the REC informed after the final attempt to collect 12-month follow-up data from the last randomised participant.

9. STATISTICAL CONSIDERATIONS

Sample Size

We expect 70% of participants to relapse between 1-12 months in UC [34], and that each RP intervention will reduce the rate to 58%, and to 48% in those receiving both. Assuming no interaction (there are rarely large interactions between behavioural and smoking replacement interventions) and comparisons between those who receive (2 arms) and do not receive (2 arms) each intervention individually then 257 participants are needed per arm to detect a difference (90% power, alpha=0.025). We plan to recruit 350 in each arm, for the primary analysis, maximizing power, but retaining sufficient power if there is evidence that participation in the EMA study may have affected outcomes and these participants need to be excluded.

Method of Analysis

Main study analysis

Statistical methods will be described in an analysis plan to be agreed and finalised prior to analysis.

The primary outcome is relapse between 1 and 12 months. The primary analysis will be intention to treat, including all those randomised and those with missing data presumed to have relapsed. Relapse is defined as smoking on 7 or more consecutive days at any follow-up point.

Abstinence is defined as reporting not smoking (allowing for slips i.e. smoking on less than 7 consecutive days at any point at follow-ups), with the additional criterion of no slip ups (not a puff) in the last month at 12-month follow-up. Biochemical verification of this latter criterion will be carried out using saliva cotinine (< 15 ng/ml [32]) for those not reporting using any nicotine product and anabasine (< 1 ng/ml [33]) for those reporting other forms of nicotine use.

Secondary outcomes will include sensitivity analyses using different criteria for sustained abstinence and different assumptions about missing cases (e.g. using the Hedeker method [35] and last known quit status), as well as analyses excluding cases with missing outcomes.

We will present baseline characteristics for the four treatment groups according to the main baseline covariate measures defined below. Analysis of the primary outcome will use logistic regression to compare the odds of relapse between treatments, with adjustment for country and SSS service or Quitline as a stratification factor. We will initially test for interaction by fitting main effects for each treatment (SR versus no SR) and (S3P versus no S3P) and the interaction between the two in the logistic regression model, tested using a likelihood ratio test of this model compared with a model with only the main effects.

If there is no significant interaction, the interaction term will be removed to obtain the main effects of each treatment, with mutual adjustment and adjustment for the stratification factors. We will adjust in sensitivity analysis for the potentially important prognostic factors we have measured at baseline to improve study power, for example number of smokers in participants' social circle, depressive symptoms, previous quitting history. We will also conduct sensitivity analysis to explore whether the assumption that those with missing follow-up data are smokers affects the study result, using the Hedeker method [35] to explore the effects of alternative assumptions.

In the case of a significant interaction, the effect of each individual intervention arm (SR only, S3P only, SR plus S3P) will be compared with the control group in logistic regression. We will also test for any interaction as a result of participation in the EMA study, and if found, restrict the main analyses to those cases not included in this aspect of the study.

Other binary secondary outcomes, sustained abstinence over 12 months and non-daily smoking, will be analysed in a similar way. Reduction in cigarette consumption will be analysed by linear regression, with transformation to normality and bootstrapping for confidence intervals if appropriate, or otherwise by non-parametric equivalent.

Prior to completion of data collection, a detailed statistical analysis plan will be drawn up, including details of any sensitivity and sub analyses, and confirmed with the Trial Steering Committee.

Cost-effectiveness analysis

Within trial economic evaluation: We will conduct a within trial incremental cost-effectiveness analysis to estimate the incremental cost per person quitting smoking based on quits at follow up and also a longer-term projection of health gains and long-term cost savings. A public-sector health care perspective will be adopted. Costs will include the cost of the trial intervention (SR and/or S3P) plus wider health care costs during the trial follow-up. Intervention costs will be collected prospectively throughout the trial by recording individual use of SR products and use of S3P and applying local unit costs to resources consumed. We will report separate estimates depending on who pays for the SR products, both during the period we have supplied and outside of it. Participants will complete a health service use questionnaire to record their use of primary and secondary health care. Published unit costs of health care will be applied to quantities recorded to estimate the total health care cost per patient. We will calculate the incremental cost-effectiveness of three active treatment arms over and above the usual care control arm. The within trial analysis will use the incremental cost per quitter as the main outcome for the cost-effectiveness analysis. We will construct cost-effectiveness acceptability curves to show the probability that each of the treatments is more cost-effective than the other three strategies. Given differences in resource costs in the two countries we will conduct separate cost-effectiveness analyses for each location using local service costs and wider health care costs.

Modelling longer-term cost-effectiveness: It is necessary also to consider longer term costs and benefits because successful quitting is expected to improve health status over a period beyond the one year trial follow up. We will therefore combine trial data and published data to model longer term healthcare cost savings and population health benefits to derive long-term incremental cost per quality-adjusted life years (QALY) estimates for the three novel intervention arms within the study versus usual care.

We will build upon previous UK health economic modelling work on smoking cessation. To estimate longer-term cost-effectiveness, we will use as a starting point the Markov cohort state-transition model developed recently by ScHARR (University of Sheffield) in a project for the NIHR HTA programme of the cost-effectiveness of cytisine vs. varenicline within the context of NHS smoking cessation services [36]. This model is an extension of the Benefits of Smoking Cessation on Outcomes (BENESCO) model [37]. Using the best available econometric analyses, the model estimates the effects of enhanced quit rates over a lifetime horizon on life years, QALYs and NHS and social care costs via long-term effects on five chronic smoking-related diseases [lung cancer, chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), stroke and asthma]. Uncertainty is examined using probabilistic sensitivity analysis; expected value of information analysis functionality enables identification of remaining uncertainties and hence research priorities.

We will develop and refine this model to meet the needs of the current RP study. We have critically reviewed the limitations of the currently implemented BENESCO

model. The key limitations are that the model does not consider that: (i) smokers might quit and relapse naturally over their lifetime, independently of intervention; (ii) individuals might succumb to more than one smoking related disease. In addition, colleagues in ScHARR have supervised a PhD student who has now completed his work to further develop the BENESCO model to incorporate the joint behaviours of smoking and alcohol use, including developing an individual level simulation that has utilised data from the Household, Income and Labour Dynamics in Australia (HILDA) Survey on longitudinal quit and relapse rates [38]. This PhD work has incorporated the natural rates of quitting and relapse and will also be available to our health economics research team to contribute to the development of the final model. On the basis of these materials, we will develop and refine the methodology, and tailor the model to the current RP trial in order to quantify the incremental cost-effectiveness of the interventions for the four treatment groups in the trial. Again, we will conduct full probabilistic sensitivity analysis and value of information analysis to quantify and prioritise remaining uncertainties and inform decision makers of their implications. We will develop both a UK and an Australian version of the model. Australian resource use and costs data will be obtained from the study for the interventions themselves and from standard routine sources for annual costs of healthcare in the different model disease states. Specific Australian prevalence rates and transition probabilities for the disease models will also be obtained as far as evidence is available. The final results will quantify the costs and benefits of the four treatment strategy options separately in a UK and an Australian setting to enable decision makers to consider fully the evidence on cost-effectiveness.

Qualitative analysis

All interviews will be audio recorded and transcribed verbatim. After familiarisation with the transcripts, the data will be indexed and imported into Nvivo 9 to facilitate systematic analysis. The initial coding frame will be based on the interview topic guides and new codes will be added as they emerge from the data during the coding process. Coded data will then be analysed using the 'Framework' method, successfully used by the applicants in previous research. This involves examining key themes from the interviews organised through 'charting' which will allow us to investigate relationships between treatment arms and successes and failures and interviewees' views and how the facilitators and barriers to the relapse prevention interventions varied by treatment group. More than one researcher will be involved in all data analysis to enhance the validity of findings.

EMA analysis

In order to explore the mechanisms through which strategies prevent relapse, EMA data will be used to examine the consequences of smoking lapses: the immediate consequences of lapses—including self-efficacy and use of coping strategies—will be used to predict time to next lapse and time to relapse (stratified by treatment group). Data collected during lapse assessments themselves will also be compared to parallel data collected during random prompt assessments to examine whether the context in which participants lapse differs by groups [39]. Additionally, we will explore group differences in the number of, and responses to, temptation episodes. EMA data will predominately be analysed using repeated measures mixed models.

10. ETHICS

In the UK, the study will be carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005

and its subsequent amendments as applicable and applicable legal and regulatory requirements.

This protocol and any subsequent amendments, along with any accompanying material provided to the participants and any advertising material will be submitted by the Chief Investigator to the UK Health Research Authority (HRA). The Australian site will apply separately to an Australian Health Ethics Committee (AHEC).

Participants will be provided with information about the main study and sub studies, including risks and benefits, via a participant information sheet, and will be given sufficient time to consider this information and ask any questions they may have. Those who wish to participate will give electronic or verbal informed consent, depending on their preference. Participants will also confirm their consent by responding to a text message. Participants who are invited and agree to take part in either of the sub studies will give additional electronic or verbal informed consent for these sub studies, separately to the main study.

Patient identifiable data will remain confidential, and will be handled, processed, stored and destroyed according to the terms of the Data Protection Act 1998. All study data collected will be stored in a secure database that will be anonymised and will not contain any identifying information, with the exception of participants' mobile telephone numbers and email addresses which need to be linked to some study data in order to send the tailored intervention texts and emails. Only study staff and representatives of the sponsor or regulatory authorities (to the extent that they are allowed by law) in each country will have potential access to view study data that could be linked to patient identifiable data.

Conflicts of Interest

Peter Hajek (CI) and Hayden McRobbie (co-investigator) have received research funding from, and provided consultancy to, pharmaceutical companies manufacturing smoking cessation medications.

Andy McEwen (co-investigator) receives a personal income from Cancer Research UK via University College London. He has received travel funding, honorariums and consultancy payments from manufacturers of smoking cessation products (Pfizer Ltd, Novartis UK and GSK Consumer Healthcare Ltd) and hospitality from North 51 who provide online and database services. He also receives payment for providing training to smoking cessation specialists; receives royalties from books on smoking cessation and has a share in a patent of a nicotine delivery device.

Stuart Ferguson (Australian site co-investigator) has consulted for GlaxoSmithKline Consumer Healthcare (GSKCH) on matters relating to smoking cessation and has received researcher-initiated project grant funding from Pfizer (through the GRAND initiative).

Ron Borland (Australian site co-investigator) works for Cancer Council Victoria which owns the IP for the version of the S3P we will adapt.

All other co-applicants have nothing to declare.

11. SAFETY CONSIDERATIONS

We expect there to be minimal possibility of harm to participants. EC and NRT use does not involve tobacco combustion, which is the primary source of the many thousands of dangerous chemicals to which smokers of conventional cigarettes are exposed. The safety profile of NRT is well established, and so far EC appear to have an acceptable safety profile also [14, 22], with no clinically significant levels of any harmful chemicals having been detected in vapour of EC [23]. Adverse events will be monitored at each follow up, and participants will be provided with a telephone number to call in between follow ups. Possible side effects will be discussed with participants, and participants are free to end SR use at any time.

12. DATA HANDLING AND RECORD KEEPING

Confidentiality

Only study personnel and the study sponsor 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), except in the case of Suspected Unexpected Serious Adverse Reactions (SUSARs), where, if additional information is required for reporting purposes, we will contact the participant by telephone to seek permission from them to do so and request their GP details.

Participants will not be identifiable from their study data, including recordings, transcripts, questionnaire data, EMA data or any written reports of the study.

All information will be kept confidential. 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.

Record Retention and Archiving

In the UK, all paper information relevant to the study will be archived and retained for 20 years at the Barts Health NHS Trust facility in Prescot Street. Electronic CRF data (which will not include personal identifiable data) will be kept on a secure online database for 20 years, following the Barts CTU's SOP on electronic archiving.

The sponsor will be informed in writing when and where all data is archived.

13. LABORATORIES

Laboratory Assessments

Central Laboratories

Cotinine and anabasine in UK saliva samples will be analysed at ABS laboratories Ltd. (Biopark, Broadwater Road, Welwyn Garden City, Herts, UK).

Sample Collection, Labelling and Logging

Samples will be labelled with participant code, date and session number. Participants reporting abstinence at 12 months will be sent a saliva swab sample kit, along with instructions on how to provide the sample and a stamp addressed envelope to return it in. Upon receipt, samples will be temporarily stored at the Health and Lifestyle Research Unit, at -20°C in a freezer suitable for biological samples. All sample collection and storing will be carried out in accordance with ABS laboratories' instructions.

Sample Receipt

All samples collected will be logged. Upon receipt of the samples, the laboratory will ensure that the physical integrity of these samples have not been compromised in transit. If they have, the CI and sponsor will be informed of this. Upon receipt of samples, laboratory staff will also ensure that all samples are accounted for as per the labelling. All samples received will be kept frozen until being analyzed.

Sample Analysis

Cotinine and anabasine in human saliva samples will be determined using high performance liquid chromatography coupled to tandem mass spectrometry with multiple reaction monitoring (LC-MS/MS) after basification of the saliva and then liquid -liquid extraction with dichloroethane using cotinine d_3 and anabasine d_4 as the internal standards. The analysis will be performed over 1 to 600ng/mL for cotinine and 0.1 to 10 ng/mL calibration range for anabasine.

Sample Storage Procedure

Samples will be frozen and stored in -20°C in freezers suitable for biological samples.

Sample destruction

When all the saliva samples have been analysed and the data has been entered, the samples will be destroyed by ABS Laboratories Ltd, in accordance with the Human Tissue Authority's Code of Practice.

14. PRODUCTS, DEVICES, TECHNIQUES AND TOOLS

Smoking Replacement (SR) Products

We will use up to three oral NRT products (e.g. nicotine mouth strips, lozenge and mouth spray or similar as per normal dosing instructions) and up to 3 types of EC (e.g. a first generation 'cig-a-like' product by non-tobacco company manufacturer and a refillable system). As this is an evolving market, it is not appropriate to choose the products in advance; however, all EC products used will have a CE mark and the e-liquid/cartridges will use pharmaceutical grade nicotine. The EC will adhere to British and Australian Standards.

Structured Planning and Prompting Protocol (S3P)

See Randomisation section for details of the S3P programme.

15. SAFETY REPORTING

Adverse Events (AE)
An AE is any untoward medical occurrence in a subject to whom the study intervention has been administered, including occurrences which are not necessarily caused by or related to the intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with study activities.

Notification and reporting Adverse Events or Reactions
If the AE is not defined as SERIOUS, the AE will be recorded in the participants' CRF and the participant will be followed up by the research team.

Serious Adverse Event (SAE)
In research other than CTIMPs, a serious adverse event (SAE) is defined as an untoward occurrence that:

(a) results in death;
(b) is life-threatening;
(c) requires hospitalisation or prolongation of existing hospitalisation;
(d) results in persistent or significant disability or incapacity;
(e) consists of a congenital anomaly or birth defect; or
(f) is otherwise considered medically significant by the investigator.

An SAE occurring to a research participant will be reported to the main REC where in the opinion of the Chief Investigator the event was:

• Related – that is, it resulted from administration of any of the research procedures, and

• Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

The following AEs are deemed to be related and expected occurrences: nausea, throat/mouth irritation and sleep disturbance.

Notification and Reporting of Serious Adverse Events
Serious Adverse Event (SAEs) occurring in UK participants will be reported by the site to the CI within 24 hours. SAEs that are considered to be 'related' and 'unexpected' by the CI will be reported to the sponsor within 24 hours of learning of the event and to the Main REC within 15 days in line with the required timeframe.

All members of the UK study team have received GCP training and are aware of the SAE reporting procedures. In the UK, upon notification of an SAE the study team member will add the details of the SAE to the QMUL Joint Research and Management Office (JRMO) SAE form and send it to the Study Manager, PI and CI for review. Once signed off by the CI the SAE form for related and unexpected SAEs will be sent to the QMUL JRMO and REC as above and the form filed in the study file. SAEs that are deemed unrelated by the CI will be recorded in the study file only.

Urgent Safety Measures
The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety. In the event that this is necessary, the measures will be taken immediately. In this instance, the approval of the REC prior to implementing these safety measures is not required. However, the CI will inform the sponsor and Main REC (via telephone) of this event immediately.

The CI will then inform the main REC in writing within 3 days, in the form of a substantial amendment. The sponsor (QMUL JRMO) will be sent a copy of the correspondence with regards to this matter.

Annual Safety Reporting
The CI will send the Annual Progress Report to the main REC and to the QMUL JRMO using the NRES template.

Overview of the Safety Reporting responsibilities
The CI/PI has the overall pharmacovigilance oversight responsibility. The CI/PI has a duty to ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

16. MONITORING & AUDITING

Monitoring will be proportional to the objective, scope, design, size, complexity and risks of the project. In the UK, the QMUL JRMO will risk assess the trial in line with the QMUL JRMO risk assessment SOP. The trial's risk assessment will be used by the Study Manager and CI/PI to create a monitoring plan (detailing the type, duration and frequency of monitoring). The risk assessment and monitoring plan will be reviewed by the Barts CTU and signed by the CI. A Copy of the plan will be kept in the TMF. The CI will ensure that the agreement/wording is not altered without written authorisation (email confirmation) from the QMUL JRMO; all new versions will be signed.

CI/study team will notify the QMUL JRMO's GCP team once the first patient has been consented onto the trial at each site.

A study may be identified for audit by any method listed below:

1. A project may be identified via the risk assessment process.
2. An individual investigator or department may request an audit.
3. A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations.
4. Projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects.
5. Projects may be randomly selected for audit by an external organisation.

Internal audits may be conducted by a sponsor's or funder representative.

17. TRIAL COMMITTEES

There will be two project sites: one based at QMUL, and the other based at Cancer Council Victoria, Australia. Each will manage their own day-to-day operations, but the project management will be overseen by the trial management group (TMG). Monthly TMG meetings will be held during the recruitment phase, moving to every two months during the follow-up phase. The TMG members will include Prof Borland and Dr Courtney from the Australian team, Prof Hajek/Prof McRobbie, Anna Phillips (QMUL Research Manager), Professor McNeill, Professor Lewis (Statistician), and a representative from the Barts CTU. Prof Hajek/Prof McRobbie will oversee the study conduct and the QMUL Research Manager will manage the day to day running. Each local team will meet weekly to ensure that recruitment is progressing according to targets.

In the UK, a Trial Steering Committee (TSC) will be convened and meet every 6-12 months. The TSC will be formed of a Chair (Independent), Chief Investigator, Study Manager, 2 service users (independent), an independent statistician, and 1-2 stop smoking service representatives or specialists in the area (at least one independent). A Data Monitoring and Ethics Committee (DMEC) will also be convened, consisting of 3 independent members – a Chair, statistician and specialist in the area. The DMEC will meet every 6-12 months.

18. FINANCE AND FUNDING

The study funder in the UK is the National Institute for Health Research, Health Technology Assessment (NIHR HTA). Public Health England (PHE) have provided the funds to cover the excess treatment costs for the UK part of the study.

The study funder in Australia is the Australian National Health and Medical Research Council (NHMRC).

19. INDEMNITY

The study Sponsor in the UK will be QMUL. The sponsor in Australia will be the Cancer Council Victoria via its Research Management section. QMUL JRMO has arranged for suitable indemnity concerning negligent harm to be in place for the study in the UK. Indemnity will be provided by QMUL in the UK.

The insurance that QMUL has in place provides "No Fault Compensation" for participants which provides an indemnity to participants for non-negligent harm.

The Cancer Council Victoria will provide indemnity for the Australian site.

20. DISSEMINATION OF RESEARCH FINDINGS

This research will contribute much needed knowledge on the efficacy of two promising interventions, and knowledge about the value of adding such interventions to usual care. The study results will also contribute to the UK and international regulatory frameworks seeking further data on use of new nicotine delivery devices in smoking cessation. Whether positive or negative, the findings will provide an important contribution to the evidence base of clinical practice and to official guidelines.

The study results will be:

a) communicated to the NIHR and published in the HTA journal;
b) published in a peer-reviewed medical journal, in Open Access format;
c) presented at international conferences on tobacco control and public health (e.g. Society for Research on Nicotine and Tobacco (SRNT) Annual Conference; European Respiratory Society Annual Congress);
d) translated for the lay audience in collaboration with our Patient Group and communicated through the QMUL press office and the UK Centre for Tobacco and Alcohol Studies in a range of press and digital formats;
e) communicated in lay format through various electronic cigarette consumer organisations (e.g. the Electronic Cigarettes Consumer Association of the UK);
f) integrated into national and international guidelines and training programmes for smoking cessation specialists. Our team works closely with the National Centre for Smoking Cessation and Training (NCSCT), advising on content and delivering several training packages;
g) directly communicated to key government, NHS, and public health stakeholders. Our team is a NICE collaborating centre, and we have previously been commissioned by the MHRA to undertake research on electronic cigarettes. Our team also includes advisors on tobacco control to the Department of Health;
h) communicated over specialist tobacco control networks (e.g. SRNT, Association for the Treatment of Tobacco Use and Dependence).

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