STUDY PROTOCOL

A multi-centred, parallel, two group, randomised controlled clinical trial, with internal pilot, to compare (i) tailored support to reduce smoking and increase physical activity as an aid to smoking reduction with (ii) brief advice to reduce or quit smoking.

A Trial of physical Activity assisted Reduction of Smoking (TARS)

Trial of physical Activity assisted Reduction of Smoking

Version 2
26th October 2017

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This protocol has regard for the HRA guidance

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1 SIGNATURE PAGE

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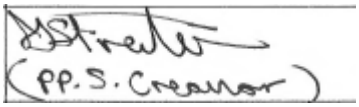
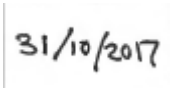
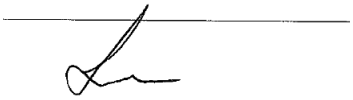
Statistician	Siobhan Creanor		
Sponsor's representative	Lisa Bowern		31st Oct 2017

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3 LIST OF ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
CO	Carbon Monoxide
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DBS	Disclosure and Barring Service
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
GP	General Practice
HIS	Heaviness of Smoking Index
HRA	Health Research Authority
HT	Health Trainer
ISF	Investigator Site File
LNCP	Licensed Nicotine Containing Products
NARS	Nicotine Assisted Reduction then Stop
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NRT	Nicotine Replacement Therapy
PA	Physical Activity
PenCTU	Peninsula Clinical Trials Unit
PI	Principal Investigator
PMG	Project Management Group
PPI	Patient Public Involvement
PROMs	Patient Reported Outcome Measures
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RA	Research Assistant
REC	Research Ethics Committee
RUQ	Resource Use Questionnaire
SAE	Serious Adverse Event
SLG	Site Leads Group
SOP	Standard Operating Procedure
SSS	Stop Smoking Service
SAU	Support as Usual
TIP	Trial Information Pack
TMF	Trial Master File
TSC	Trial Steering Committee

4 STUDY SUMMARY

Study Title	A multi-centred, parallel, two group, randomised controlled clinical trial, with internal pilot, to compare (i) tailored support to reduce smoking and increase physical activity as an aid to smoking reduction with (ii) brief advice to reduce or quit smoking.
Study Design	A multi-centred, two arm, parallel group, randomised controlled trial with internal pilot.
Study Participants	Adult smokers (aged ≥18) who wish to reduce their smoking, but have no immediate plan to quit.
Intervention	Supported smoking reduction, integrated with physical activity.
Control	Usual care (NICE guidelines). Brief advice on stopping smoking, or referral to NHS Stop Smoking Services.
Study duration	44 months
Nº of participants	900 participants randomised 1:1 to receive intervention (n=450), or control (n=450).
Setting	Suitable smokers will be recruited from primary health care and the community, and randomised to receive usual care, or the study intervention.
Aims	To determine if supporting smokers (who do not want to quit immediately) to reduce smoking and increase physical activity results in a reduction in smoking, and of those who do decide to quit, how many remain abstinent for at least 12 months, compared to those receiving usual care.
Primary Outcome	Carbon monoxide (CO) verified prolonged abstinence over 6 months
Secondary Outcomes	• CO verified abstinence at 3, 9 and 15 months post baseline. Only those reporting abstinence by mailed survey at 3 and 9 months will be contacted for CO verification. Only those abstinent at 9 months will be followed up at 15 months if supported by a futility analysis. • Self-reported physical activity (7-day physical activity recall) • Urge & strength of urge to smoke • Self-reported smoking (and calculated costs) • Use of e-cigarettes and NRT (nicotine replacement therapy) products • Health related quality of life (EQ-5D-5L & SF12) • Physical activity (accelerometer) (7 days) • Self-reported height and weight (BMI) • Health service utilisation and costs
Process outcomes	• Importance and confidence in smoking reduction and cessation • Importance and confidence in being physically active • Availability of support to reduce smoking and increase physical activity • Use of physical activity for smoking regulation • Planning to change smoking and physical activity • Self-monitoring of smoking and physical activity • Recruitment and intervention engagement processes (mixed methods)
Inclusion criteria	• Adult smokers wishing to reduce but not quit in the next month • ≥ 18 years • ≥ 10 cigarettes per day (for at least 1 year). Irrespective of use of other nicotine containing products. • Able to give informed consent
Exclusion criteria	• Unable to walk unaided for at least 15 min • Any illness or injury that might be exacerbated by exercise • Unable to engage in the study and/or intervention due to language or other reasons (eg, provide an unacceptable level of risk to the Health Trainer or research team members). All ineligible participants will be referred for advice in line with usual practice.
Timepoints	Set-up 8 months, recruitment, intervention and follow-up 27 months, analysis & write-up 9 months. 44 months total study duration

5 BACKGROUND AND RATIONALE FOR THE PROPOSED STUDY

5.1 Rationale

Despite falling prevalence, smoking remains the main cause of preventable morbidity and premature death in England, and makes a growing contribution to health inequalities [7]. An ASH commissioned report [8] indicated that the total cost to society of smoking in England is £13.9b, including £2b to the NHS. Tobacco control policies and individually targeted interventions have helped to reduce population smoking prevalence to about 17.0%, but varying considerably by socio-economic and mental health status [9]. Among those initially motivated to quit, after one year, only 4% of those attempting alone succeed, increasing to c.7% with NHS primary care support and c. 15% with pharmacological and behavioural support in a NHS Stop Smoking Service (SSS) [10]. NICE PH10 guidelines [5] for smoking cessation focus on identifying a quit date and abrupt cessation. This is recommended with pharmacological and behavioural support because smokers cutting down prior to quitting may gain greater reward from each cigarette and hence find quitting even more difficult [11].

Yet, in the English Smoking Toolkit Study (between 2011 and 2014), 50% of smokers claimed to be cutting down, of whom 63% were using no nicotine products or e-cigarettes [12]. In a US survey interest in reduction in smoking was highest among those who were less interested in quitting and heavier smokers [13]. Also, smokers who do not intend to quit in the next month, but who cut down with the use of nicotine replacement therapy (NRT), are more likely to make a quit attempt and be abstinent at follow-up [14]. NICE PH 45 guidelines [3] extend the options for smokers who do not immediately wish to quit smoking, by using behavioural strategies with licensed nicotine-containing products (LNCPs). However, both the NICE review [3] and a previous one [15] identified a need for further research to identify effective behavioural approaches for smoking reduction, which may increase quit attempts. Specifically, Asfar and colleagues [15] identified 6 trials of pharmacological interventions, 3 trials of combined behavioural and pharmacological interventions, and only one involving a multi-level behavioural support package (focusing on reduction rather than cessation, with some limited effects).

There has been a marked increase in the use of e-cigarettes, with some low grade evidence that e-cigarette use may lead to smoking cessation and reduction [16]. However, data from recent surveys suggest that the effects may be moderated by how e-cigarettes are used. Only daily use compared with less frequent use of e-cigarettes increases the number of quit attempts and reduction in smoking, and that daily or non-daily e-cigarette use does not increase cessation rates [17], except for those using a version of e-cigarettes called tanks on a daily basis [18]. The NICE review did not recommend the use of e-cigarettes for those smokers not immediately wishing to quit but who do wish to reduce, but did recommend the use of licensed nicotine containing products for this group. The encouraging exploratory findings in a pilot study [1,2] involving an intervention with behavioural support for smoking reduction and increasing physical activity were not available for the NICE review [3].

5.1.1 Why reduction programmes may work

Cigarette smoking leads to neural processes involving the formation of conditioned relationships between environmental and internal stimuli and smoking. A reduction in smoking may disrupt these relationships so that cues are less likely to trigger an urge to smoke [19] and can be achieved by structured scheduling of smoking. This may involve having specific sequential goals for either

reducing cigarettes per day or reducing smoking periods. Other mechanisms involve the following: (1) Increasing the length of time between cigarettes may reflect steps in moving from the identity of a heavy or moderate smoker to that of a light then non-smoker. Identity shifts are important in smoking cessation; (2) Increasingly longer periods between smoking a cigarette may progressively raise confidence to abstain, which may generate intentions to actually quit and reduce the risk of relapse; (3) A lower drug intake might reduce drug dependence increasing the ability to abstain completely. Nicotine assisted reduction then stop (NARS) programmes and the use of LNCPs aim to facilitate these changes by providing a dose of nicotine to relieve cravings and withdrawal symptoms.

5.1.2 Use of reduction approaches & perceptions about smoking reduction

Since our pilot trial of exercise assisted smoking reduction recruited in 2011/12 [1], use of any nicotine product has increased from just under 20% to about 30% in late 2015 [20]. Increases were mostly related to shifts in use of e-cigarettes (which were used less frequently by lower socio-economic groups) [20]. While use of e-cigarettes may be levelling off, it may be that smokers may be becoming disillusioned with the lack of success in quitting with the use of nicotine products, or there is a fear among a significant proportion (c. 25%) that the use of e-cigarettes does not remove the risks to health from smoking [21–23]; though there is no evidence that such products carry health risks at present, at least in the short term [16, 24, 61]. Some smokers also identify smoking with the maintenance of mental health, and associate smoking reduction with adverse effects, but there is no evidence at present that reduction and cessation adversely effects mental health [25]. There is evidence that without a clear reduction programme LNCPs can maintain an addiction by providing similar doses of nicotine as a cigarette, with similar reductions in withdrawal symptoms and urges to smoke, and satisfying experience [26]. Moreover, dual use of combustible cigarettes and electronic cigarettes or LNCPs is increasingly common but there is evidenced that this dual use does not reduce levels of carcinogens relative to smoking only combustible cigarettes [61]. There is also evidence that smokers typically underuse such products, which may limit their potential to promote smoking cessation [12].

In summary, from the above paragraphs, there remains scope to explore how behavioural strategies, including the promotion of physical activity can aid smoking reduction and ultimately cessation.

5.1.3 Physical activity (PA) as an aid to smoking reduction & cessation

While evidence [4], from adequately powered trials, suggests that increasing exercise as an adjunct to standard stop smoking cessation programmes may have long term benefits on quitting, further research is needed on the value of promoting physical activity for reducing smoking (and quitting) for smokers who do not immediately wish to quit. In the present context there may be two types of processes involved in how increases in physical activity influences smoking reduction and cessation, namely implicit and explicit ones. Implicit processes may be involved particularly if the focus is on increasing PA, rather than smoking reduction. For example, increasing PA may enhance mood and reduce stress, which reduces the urge to smoke. Explicit processes may be involved if the focus is on how best to cut down smoking, or support a quit attempt, specifically using PA. For example, exercise sessions (eg, aerobic exercise) could help to manage cravings and withdrawal symptoms or weight management.

5.1.4 Theoretically, increasing PA may help reduction of smoking in several ways

1) Reviews (eg, Ussher and colleagues); including 41 studies [4]) with meta-analysis [27] have shown a consistent reduction in urges to smoke and withdrawal symptoms, during and following exercise (for up to 30 minutes) compared with being passive. Encouragingly, findings suggest relatively convenient forms of physical activity (e.g. 10 to 15 minutes of brisk walking) can be effective, particularly at a time when cravings are moderate to high, following a period of abstinence. PA also appears to reduce reactivity to smoking cues, which have been shown to predict lapses and relapse during a quit attempt [28], and delays ad libitum smoking. [28–31] PA may have neurobiological effects as suggested by functional Magnetic Resonance Imaging [32], and decreases in salience (shown by reduced attentional bias, using eye tracking technology) of smoking related stimuli [33]. In parallel work, animal research consistently suggests that exercise acutely reduces self-administered addictive substances [34] through neurobiological processes [35–37].

2) Increasing PA while cutting down (then quitting) may reduce weight gain. In prospective population surveys and trials weight gain and fear of weight gain is associated with reluctance to quit smoking and remain abstinent, especially among women and initially heavier smokers [38–40], with an average of 7kg gained within a year of quitting [41]. Increasing PA has been suggested as a useful strategy to prevent weight gain [42], not only by increased energy expenditure, and metabolic rate, but also through self-regulation of energy intake, particularly emotional snacking [43] in response to withdrawal symptoms such as depression and anxiety [44, 45].

3) As a result of increasing PA a smoker may begin to establish a different identity (eg, investing in personal fitness and improved respiratory function, and generally becoming a “healthy person”), which in turn may trigger a desire to reduce harm from smoking through reduction and ultimately quitting [1].

5.1.5 Chronic effects of exercise as an aid to smoking cessation among those who wish to quit

A recent systematic review [4] of the effects of an exercise or physical activity promotion intervention on smoking cessation identified 20 trials with a total of 5,870 smokers wishing to quit. Most trials had important methodological limitations, including small samples sizes (eight trials had fewer than 30 people in each treatment arm). Studies varied in the timing and intensity of the smoking cessation and exercise programmes offered. Among the more rigorously conducted trials, four studies showed significantly higher abstinence rates in a physically active group versus a control group at end of treatment. One of these studies also showed a significant benefit for exercise versus control on smoking cessation at the three-month follow-up and a benefit for exercise of borderline significance ($p = 0.05$) at the 12-month follow-up, but this involved a vigorous structured exercise programme which may not be widely acceptable to smokers wishing to quit. Another study reported significantly higher abstinence rates at 6 month follow-up for a combined exercise and smoking cessation programme compared with brief smoking cessation advice. One study showed significantly higher abstinence rates for the exercise group versus a control group at the three-month follow-up but not at the end of treatment or 12-month follow-up. The other studies, and one more recently published with pregnant smokers [46] showed no significant effect of exercise on abstinence rates. In summary, for smokers who want to quit, physical activity can be integrated into standard behavioural support for smoking cessation [47–50] and can increase smoking cessation, at least until the end of the intervention, in the most rigorous studies.

5.1.6 Chronic effects of exercise as an aid to smoking reduction among those who don't wish to quit

A recent pilot trial [1], conducted by the applicants, randomised 99 smokers, who wished to reduce smoking but not quit, to receive advice on smoking reduction/cessation (control) or client-centred behavioural support (by phone or face-to-face) for smoking reduction and increasing physical activity (intervention). Exploratory analysis [52] revealed the intervention group, compared with control, were significantly more likely to achieve at least 50% reduction in number of cigarettes smoked (39% vs 20%), to attempt to quit (22% v 6%), be abstinent up to 8 weeks after quit day (14% vs 4%), and be abstinent at 16 weeks (10% vs 4%). A higher proportion of the intervention group also reported using physical activity for controlling smoking: 55% vs 22% and 37% vs 16%, at 8 and 16 weeks, respectively. Delivery of the intervention was regarded by both providers and recipients as feasible and acceptable, with the focus on reduction rather than cessation being a particularly valued aspect, and important for trial recruitment [2]. The participants used a variety of behavioural smoking reduction strategies, sometimes supported with changes in physical activity, to control cravings [51]. Exploratory cost-effectiveness analyses, using data from the pilot trial, indicated that, if the results were replicated, the intervention would be considered cost-effective in an NHS setting. The study also provided valuable information about trial recruitment [52], retention [53] and intervention engagement [1] and fidelity [54]. In the pilot study, smokers were excluded if they wished to use NRT and survey data [12] suggest up to 25% of smokers would now be ineligible (for the proposed study) if we excluded smokers using either NRT or e-cigarettes in the proposed study. This would be a sizeable proportion and their exclusion may limit the generalisability of the findings, as well as adding constraints on recruitment. Further reviewing of the literature suggests that exercise still acutely reduces cravings while using NRT [55], and smokers often use a combination of pharmacological and behavioural approaches for reduction. We therefore propose to include those using NRT and e-cigarettes in this definitive study. By assessing self-reported use nicotine products and engagement in physical activity we will conduct sensitivity analyses to examine the impact of NRT/e-cigarette use on the findings.

5.1.7 Why the research is needed now

Smoking cessation results in a wide range of health benefits, and reduces preventable health care costs [5]. For those who do not immediately wish to quit, there is some evidence that smoking reduction approaches, almost exclusively from pharmacological trials, can lead to not only lower consumption of tobacco but also more attempts to quit smoking [56]. A NICE Review [3] identified an urgent need for more evidence for the effectiveness and cost-effectiveness of behavioural interventions (with and without pharmacological support) for smoking reduction, cessation induction and long-term cessation, for those wishing to reduce smoking but not quit. Given that physical activity interventions can reduce weight gain after smoking cessation [57], increase smoking cessation [4], and possibly support smoking reduction and induce quit attempts and cessation among those not initially ready to quit [2] there is a strong need to confirm the latter finding through a definitive trial. The value of the proposed intervention may be considerable as new ways are sought to improve multiple health behaviour change [7]. While smoking reduction and quitting is the primary focus of the proposed research, an intervention that also increases health enhancing physical activity is likely to have additional physical and mental health benefits, especially since smokers tend to be less physically active [58]. Physical activity enhances mood and behavioural interventions with mood management components can increase long-term quit rates [59].

In summary, there is an urgent need for research involving behavioural and pharmacological approaches to reduce smoking among those not immediately ready to quit. But currently there is little or no evidence that reduction is a useful outcome in facilitating cessation and improving health. This study investigates CO-confirmed prolonged abstinence over 6 months as the primary outcome rather than a measure of smoking reduction (although this is a secondary outcome) because a 'hard' outcome is likely to have greater impact on the evidence (and guidelines), with smoking cessation still regarded as the number one goal to improve health outcomes. The choice of 9 months post-baseline (ie, 6 months post intervention) for the primary end-point will ensure the trial will contribute to the most rigorous evidence base for smoking cessation, such as Cochrane reviews. This study allows for a 15 month post baseline follow-up to confirm long-term biochemically verified prolonged abstinence.

6 AIMS AND OBJECTIVE

The overarching research question is whether in addition to the usual standard support, a client-centred intervention with behavioural support to reduce smoking and promote physical activity, for smokers wishing to reduce smoking with no immediate plans to quit (but who may be open to the notion of quitting), can increase CO-confirmed prolonged abstinence at 9 months post baseline (i.e. 6 months post intervention) compared to standard support alone, and whether such an intervention is cost-effective.

The aims of the trial are as follows:

- To determine whether the additional behavioural support for an intervention promoting smoking reduction and increasing physical activity, compared to support as usual (SAU), significantly increases the proportion of participants who achieve prolonged abstinence at 9 months post baseline as confirmed by the concentrations of their expired CO.

- To determine whether the intervention, compared to SAU, increases the proportion of participants who reduce self-reported cigarette smoking by at least 50% at 3 and 9 months post baseline compared to baseline smoking levels, while quantifying the use of licenced nicotine containing products (LNCPs) and e-cigarettes.

- To determine whether the intervention, compared to SAU, increases the proportion of participants who achieve CO-confirmed prolonged abstinence at 15 months post baseline (i.e., 12 months post intervention).

- To determine whether the intervention, compared to SAU, increases self-reported physical activity at 3 and 9 months post baseline, and accelerometer assessed physical activity at 3 months post baseline.

- To determine whether the intervention, compared to SAU, improves quality of life (SF 12, EQ-5D-5L), weight and cigarette cravings at 3 and 9 months post baseline.

- To estimate the additional resource use and costs of delivering the intervention and to estimate the differences in health and social care service utilisation and the related costs between intervention and SAU at 9 months post baseline.

- To estimate the cost-effectiveness of the intervention compared with SAU at (i) 9 months (incremental cost per unit change in abstinence rate, and cost per quality adjusted life year [QALY] gained) and (ii) over a longer term / lifetime horizon (incremental cost per life year saved, per QALY gained) extrapolating beyond the trial using a previously developed decision-analytic model to estimate future costs and benefits.

- To quantitatively and qualitatively determine if the effect of intervention is modified by age, gender, socioeconomic status, or baseline smoking characteristics.

- To quantitatively and qualitatively explore the mechanisms through which the intervention may impact on the outcomes, through a mixed methods process evaluation, based on a logic model for how the intervention is expected to have the proposed effects.

- To determine if the intervention, compared to SAU alone affects importance and confidence to reduce smoking and increase physical activity.

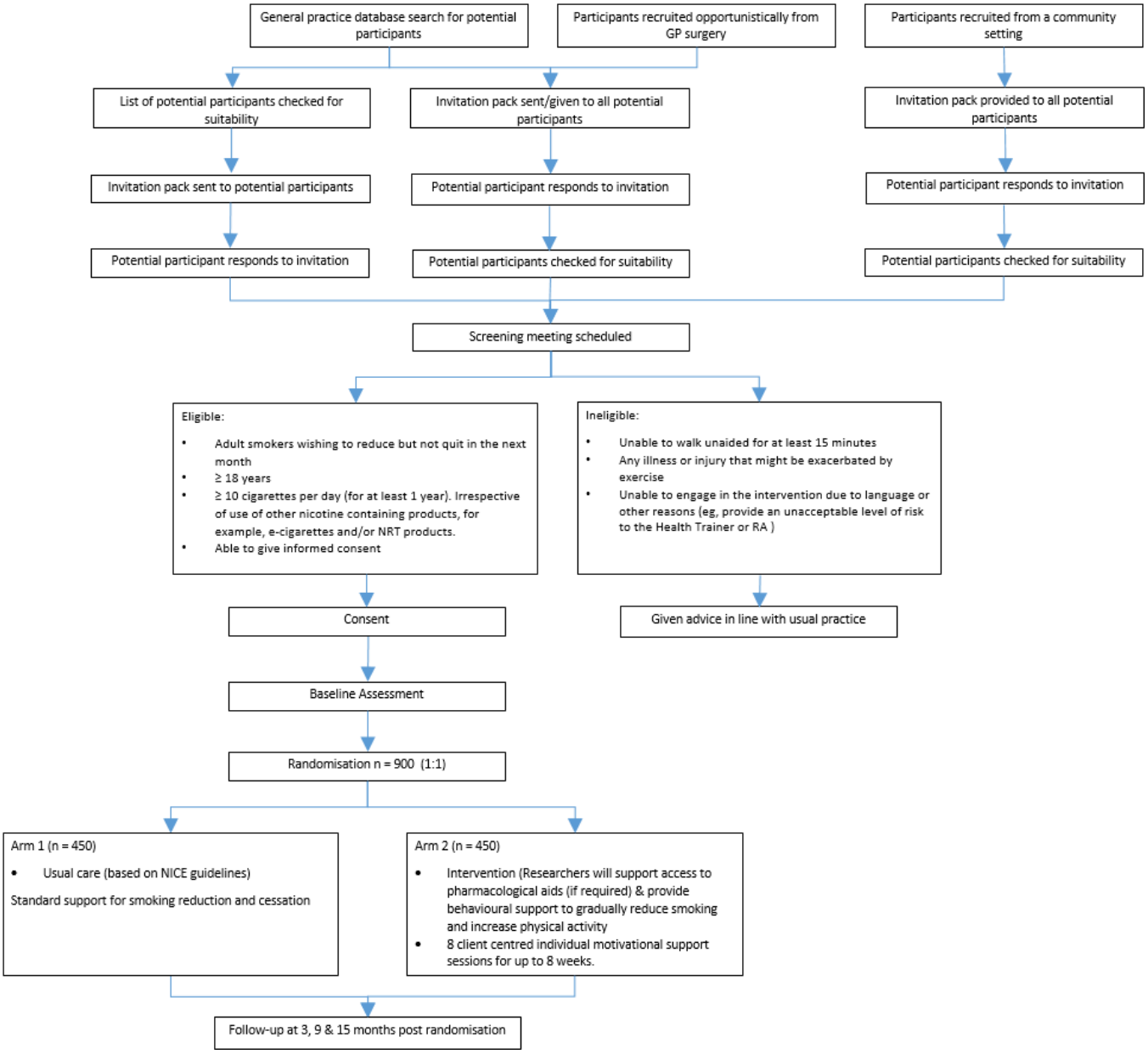
- To determine if the intervention, compared to SAU alone increases perceived availability of support to reduce smoking and increase physical activity.

- To determine if the intervention, compared to SAU alone increases planning to change smoking behaviour, physical activity and self-monitoring.

7 TRIAL DESIGN

This is a multi-centre, randomised controlled study of participants recruited via primary care, and the community, who wish to reduce their smoking, but have no immediate plan to quit. Following written consent and completion of baseline measures, 900 participants will be randomly allocated in a 1:1 ratio to either the intervention or control arm. Randomisation will follow permuted blocks, stratified by recruitment site, and the score from the 2-item Heaviness of Smoking Index (HSI) [74].

7.1 Trial schema



7.2 Study personnel

The study will be led at each of the four collaborating University sites (Plymouth University, Nottingham University, St George's University of London, and Oxford University) by a local Principal Investigator.

All study personnel undertaking home visits will be asked to comply with their employers' lone working policy. All staff working with study participants will be required to complete Disclosure and Barring Service (DBS) checks, as they may be working with vulnerable individuals.

Health trainers will be part of the research team and trained to support participants in the intervention. They will be line managed by the site PI and receive training and supervision by a member of the lead site research team.

7.3 Docmail®

Sites will be allowed to use Docmail® during the study for mailing out study related correspondence to participants.

7.4 Primary outcome

Carbon monoxide (CO) verified prolonged abstinence over 6 months

We will use guidance provided by Aveyard *et al* (2009) [75] on floating prolonged abstinence. Study participants who report abstinence on the 3 month mailed survey (which is confirmed by face to face CO expired air assessment) and then again self-report abstinence (and not having smoked even a puff since the 3 month assessment) on the 9 month mailed survey (which is again confirmed by CO expired air assessment), will be identified as having prolonged abstinence over at least 6 months.

The CO monitor used in this study is a Bedfont Micro CO monitor. The CO measurement involves the participant holding their breath for 10-15 seconds, and then blowing into the monitor. The carbon monoxide value in parts per million (ppm) is shown with values below 10 ppm indicating abstinence**.** The reading at each recruitment site will be reported remotely into the on-line PenCTU data management system. The CO monitor will be regularly calibrated to ensure accurate measures.

7.5 Secondary outcomes

Point prevalence CO verified abstinence at 3, 9 and 15 months post baseline

Only those reporting abstinence by mailed survey at 3 and 9 months will be contacted for CO verification. Only those abstinent at 9 months will be followed up at 15 months by mailed questionnaires and if abstinent by face-to-face assessment of expired CO.

Self-reported smoking and use of aids to reduce/quit smoking

Study participants will be asked to self-report the number of cigarettes smoked and type of nicotine product, i.e. pipes, cigars and roll your own. The same formula used in the EARS pilot study will be used to convert amount of loose tobacco into number of cigarettes [1].

Questions to capture use of e-cigarettes and NRT (nicotine replacement therapy) products

Physical activity

Questions at baseline, 3 and 9 months will assess self-reported 7-day physical activity recall.
A sub set of all participants in the TARS study will be invited to wear an accelerometer for a 7 day period during the study. The accelerometer, and instructions for use will be mailed to selected participants at the 3 month time point from CTU, along with the 3 month questionnaire booklet. The accelerometer is waterproof, and is worn continuously for 7 days. At the end of the 7 days the participant should return the accelerometer to the CTU in the freepost envelope provided.

Self-reported height and weight – Body Mass Index (BMI)

At baseline, 3 and 9 months participants will be asked to self-report their height and weight. The questions will be part of the questionnaire booklet mailed to participants from CTU at baseline, 3 and 9 months. Based on the weight and height reported we will derive a measure of BMI.

Health related quality of life (EQ-5D-5L & SF-12)

EQ-5D-5L

This is described in section 19.1.

SF-12

The SF-12 is a 12-item, patient-reported survey of patient health, consisting of twelve questions [70]. In this study participants will be asked to complete the SF12 as part of the questionnaire booklet mailed to them from CTU at baseline, and then at 3 months follow-up and 9 months follow-up.

Health economic outcomes

Health service utilisation and costs, including smoking related costs

Process measures

The following process measures will also be assessed as part of the self-report questionnaire booklets issued to all participants by CTU at the baseline and 3 months:

- Importance and confidence in smoking reduction and cessation
- Importance and confidence in being physically active
- Availability of support to reduce smoking and increase physical activity
- Use of physical activity for smoking regulation
- Planning to change smoking
- Planning to change physical activity
- Self-monitoring of smoking
- Self-monitoring of physical activity
- Urge & strength of urge to smoke

8 TRIAL PARTICIPANT SELECTION

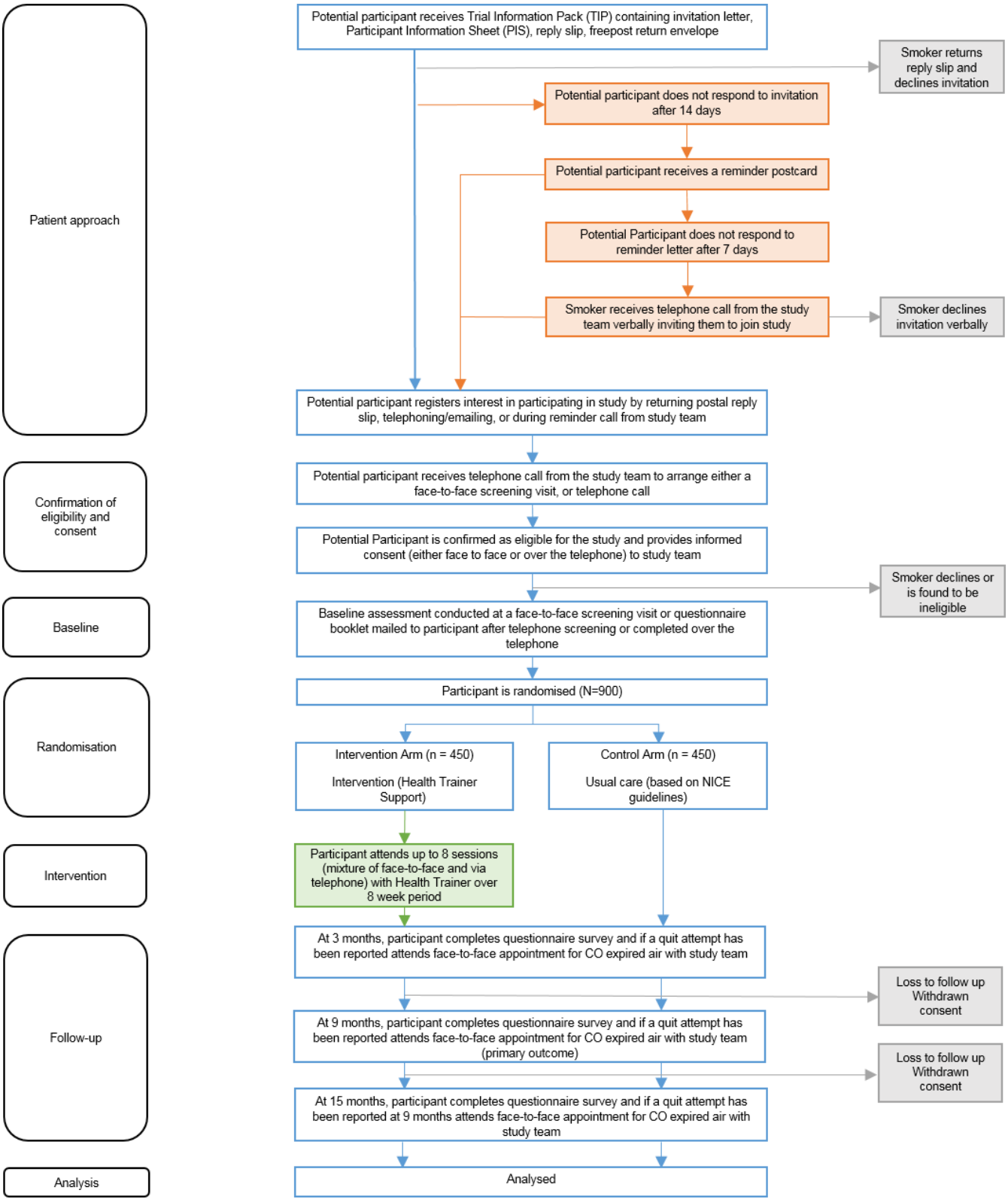
8.1 Target population

Adult smokers wishing to reduce the amount they smoke, but with no immediate plans to quit, recruited from GP surgeries and the community based around four collaborating University sites: Plymouth, Nottingham, Oxford and St. George's (South London).

8.2 Number of participants

A total of 900 participants will be recruited.

8.3 Example participant pathway



8.4 Inclusion criteria

- Adult smokers wishing to reduce but not quit in the next month
- ≥ 18 years
- ≥ 10 cigarettes per day (for at least 1 year). Irrespective of use of other nicotine containing products, for example, e-cigarettes and/or NRT products.
- Able to give informed consent

8.5 Exclusion criteria

- Unable to walk unaided for at least 15 min
- Any illness or injury that might be exacerbated by exercise
- Unable to engage in the study and/or the intervention due to language or other reasons (eg, provide an unacceptable level of risk to the Health Trainer or research team members).

All ineligible participants will referred for advice in line with usual practice.

8.6 Participant identification, screening and consent

8.6.1 Sites

Two types of sites will take part in this study:

Collaborating sites: The four university sites (Plymouth University, Nottingham University, St George's University of London, and Oxford University) where the PIs are based.

GP practices: These will be located in the geographical area surrounding each of the four collaborating sites, and are where potential study participants will be identified.

8.6.2 Participant identification

Potential participants will be identified at either a GP practice, or from the community, in the geographical areas surrounding the four collaborating sites. Special consideration should be given to selecting participants that live within manageable travelling distance of the collaborating sites, to enable participants to easily access the study intervention, and assessments.

Potential participants will be identified in more than one way, as local practice varies between collaborating sites and participating GP practices.

Participants identified at a GP practice: At participating GP practices, participants will be identified either from a search of the general health practice database by a member of the local research team, typically a research nurse or a research associate, or by opportunistic approaches or surgery adverts. The type of database used may vary depending on local practice. Alternatively, participants will be identified opportunistically face-to-face at the GP surgery by a member of the local research team, such as a GP, research nurse or research associate.

Participants identified in the community: Potential participants will be identified by a member of the local research team. This may include, but is not limited to; local stop smoking services and local employers.

8.6.3 Participant information

All potential participants will receive a trial information pack (TIP). The TIP will contain a patient information leaflet, an invitation letter, a reply slip, and a prepaid return envelope. The information pack will contain a telephone number, and e-mail address for potential participants to contact if they would like to discuss the study in more detail with a member of the local research team, before deciding whether to participate.

Potential participants will either receive the TIP in person, or through the post from a member of the local research team. The method used to distribute TIPs will depend upon the circumstances of the potential participant and local practice.

Anyone not replying to the invitation letter may also receive a reminder postcard and a follow-up telephone call from the local study team, such as an administrative member of the GP practice, subject to local permission. Follow up phone calls are an effort to address health inequalities, so that those with low literacy levels are not excluded because they are unsure what is being offered to them. This approach was approved in the ethics submission for the pilot EARS trial.

8.6.4 Screening and consent

When a completed reply slip (or equivalent expression of interest) is received from a potential participant, a member of the local research team will contact the interested participant using the details specified by the participant, to arrange either a telephone call, or a face-to-face screening/consent meeting. The format and location of the screening/consent meeting will depend upon local practice, and the preferences of the potential participant. A suitably trained member of the local research team will outline the study, answer any queries, determine eligibility, obtain consent, administer and arrange for the participant to receive a baseline assessment booklet.

Participants will receive their information leaflet prior to the screening assessment in order to allow sufficient time for consideration of participation, although if participants want to consent straight away, that will also be acceptable, as long as the person taking consent is confident that the potential participant has understood the study. Informed consent will be obtained by a suitably qualified member of the local research team, prior to screening, or any study procedures being undertaken.

All participants will also be asked to agree to their GP being informed of their involvement in the study. This may be any GP practice, and not necessarily, one identified in the study REC/HRA application.

8.6.5 Face to face consent process

The face-to-face screening/consent appointment will take place at a public location (i.e. not the participants home) acceptable to both the potential participant and the member of the local research team, examples include, but are not limited to; GP practice, University meeting room, and public meeting place, such as a coffee shop. At this meeting the local research team member will describe the study, answer any questions, and check final eligibility for the study. Potential participants who are willing and eligible to take part will be asked to complete, sign and date the study consent form, which will also be signed and dated by the person obtaining consent. A copy of the signed consent form will be given to the participant, a copy will be sent to the CTU, and the original signed form will be retained in the Investigator Site File. Following receipt of valid consent the local research team member will issue the baseline questionnaire booklet, which the participant can either complete at

the face-to-face screening/consent meeting, or take away and post to the CTU using the freepost envelope provided. If the baseline questionnaire booklet is completed at the face-to-face screening/consent meeting, it must be returned to CTU using an agreed process.

8.6.6 Telephone consent process

If the potential participant is unable or unwilling to meet with a member of the local research team in person, consent can be obtained via the telephone. Participants will be provided with the same information as in the face-to-face process (above) and given the opportunity to have any questions answered. If participants are willing and eligible to take part, a member of the local research team will read out the separate elements of the consent form and get the patient's verbal assent for each one. The researcher should initial each box on the consent form to indicate that each clause has been read to and agreed by the participant. The local research team member should sign and date the consent form. A copy of the signed consent form will be sent to the participant, a copy will be sent to the CTU, and the original signed form will be retained in the Investigator Site File. Given the nature of the study, there is no requirement for participants to sign the consent form themselves in the case of telephone consent. Upon receipt of valid consent the local research team member will post the baseline questionnaire along with a cover letter and prepaid return envelope to the participant, or continue to administer the baseline assessments by phone following screening, or at a later arranged time.

8.7 Baseline

Following receipt of informed consent study participants will be invited to complete baseline assessments. The baseline assessments will either be completed at a face-to-face screening/consent visit (as described above), or be mailed to participants in the form of a questionnaire booklet, with a cover letter, and freepost return envelope. If the booklet is mailed to the participant the opportunity will be given for participants to complete the questionnaire booklet over the telephone with a member of the local research team, if they would prefer. Randomisation will depend upon CTU receiving a completed baseline questionnaire booklet from the potential participant. A shopping voucher will be mailed to all participants upon CTU receipt of the completed baseline questionnaire booklet.

The baseline questionnaire booklet contains questions relating to the following:

- Smoking behaviour
- Importance and confidence in smoking reduction and cessation
- Importance and confidence in being physically active
- Availability of support to reduce smoking and increase physical activity
- Use of physical activity for smoking regulation
- Self-reported physical activity (7-day physical activity recall)
- Planning to change smoking
- Planning to change physical activity
- Self-monitoring of smoking
- Self-monitoring of physical activity
- Urges & strength of urge to smoke
- Use of e-cigarettes and NRT (nicotine replacement therapy) products
- Health related quality of life (EQ-5D-5L & SF12)
- Self-reported height and weight (BMI)
- Health service utilisation and costs, including smoking related costs

- Self-reported health & social care utilisation costs

8.8 Randomisation

Participants will be individually randomised to either the intervention, or control group (1:1 ratio) following consent, and completion of baseline assessments, to ensure concealment is preserved. Randomisation will be achieved by means of a 24-hour web-based system created by the Peninsula Clinical Trials Unit (CTU) in conjunction with a statistician independent from the trial team, and will use random permuted blocks, with stratification for recruitment site, and a dichotomised low/high score from HSI. The randomisation website will incorporate a brief online case report form (CRF) that, when required details have been completed, will allow randomisation. The CTU programming team will run checks before and during the trial to verify the integrity of the randomisation system.

It is not possible to blind participants to their allocated group. Every effort will be made to ensure that the trial team (including the researcher who is collecting follow-up CO measures at each site), remain blind to the allocation of each participant when collecting follow-up data. It is possible that participants will disclose if they have received support to reduce smoking prior to such an appointment. Health trainers delivering the intervention will also obviously be aware of the participant's allocation to trial arm, and they will be discouraged from communicating with site researchers about this. Questionnaire booklets and accelerometers will be mailed out from and returned to the CTU without knowledge of the trial arm allocation.

Following randomisation all participants will be sent a letter from CTU confirming which trial arm they have been assigned to, and a guidance sheet on usual support locally for smoking reduction and cessation. The participants GP will also be sent a letter notifying them that one of their patients is participating in the study.

9 INTERVENTION

9.1 TARS Intervention

Participants in the intervention arm will be offered open-ended support from a Health Trainer (HT) which will broadly include the content described in Table 1 below. In the interests of ensuring it meets the participants needs the HT will suggest options for the support provided but empower the participant to decide what support is offered, where and when. In the pilot EARS trial participants had an average 4.2 sessions by phone or face to face with the HT with a range of 0-8 [1]. If a smoker wishes to quit at any time during the 8 week intervention period, they will be offered 6 weeks of additional behavioural and motivational support from the HT, as well as support to access services as part of usual care to stop smoking (as available at each location) if desired. If a smoker wishes to reduce smoking using e-cigarettes or licenced nicotine containing products (LNCP) they will also be offered any local available support for this. Typically, there are no formal programmes for use of medication during reduction and people usually buy their own NRT or, more often, e-cigarette or vaper product. We will also monitor any national guidelines (eg, NICE PH45 guidelines for smoking harm reduction) for any changes and adopt our actions and guidance accordingly throughout the trial.

The goal of the intervention is to promote motivation to make a quit attempt. If a smoker wishes to quit at any time during the 8 week intervention period, they will be recommended to attend a stop

smoking service, where they will be offered and pharmacological and behavioural support that comprises usual smoking cessation practice. If the participant prefers, the health trainer could continue to provide cessation support and recommend options for use of pharmacotherapy.

Intervention components	**Aim**	**Content**	**Process and outcome evaluation**
Active participant involvement (1)	Develop rapport, build trust, and shared respect.	Effective communication skills. Build autonomous support.	Participant feedback on HT-led support.
Build motivation to reduce smoking (2) and increase PA (3)	Identify ambivalence towards reduction & quitting. Build self-awareness & confidence to cut down and increase PA.	Help smoker to identify importance & challenges of reduction & cessation, and implicit & explicit roles of PA. (motivational interviewing techniques).	Smoker has desire and confidence to cut down and perhaps quit over the early sessions, and increase PA. Smoker engages in more self-monitor of smoking and PA behaviour.
Set goals to reduce smoking (4) and increase PA (5)	Develop strategies to reduce smoking and increase PA.	Set SMART goals to reduce smoking and increase PA. Signpost to PA opportunities & remove barriers to do PA.	Goals identified and action plans developed. Smoker engages in more goal setting to reduce smoking and increase PA behaviour.
Review/problem solving for smoking (6) & PA (7)	Build confidence, perceptions of control, & self-regulation skills.	Smoker reflects on smoking reduction and PA, identifies barriers and possible solutions, increases and sets new targets; perhaps to quit.	Goals revised to reflect confidence to increase PA, reduce smoking, and possibly quit.
Integrating idea of changing smoking and PA (8)	To help smoker to identify any links between smoking and PA	Explore with smoker how PA may influence smoking (and vice versa) (person centred exchange of information (Ask-Tell-Discuss)).	Smoker increases use of PA as an aid to smoking reduction.
Reinforce health identity shift (9)	To help identify shift from smoker to healthier identity.	Smoker reflects on label as heavy – moderate – light or non-smoker status, and more active person.	Decrease in importance of smoking and increase in importance of doing PA identified.
Manage social influences on smoking (10) and PA (11)	To involve others in process of reducing smoking and increasing PA. Manage negative or undermining social influences.	Smoker identifies key others who can support reduced smoking (or cessation) and increasing PA, and engages with them in preferred ways. Uses negotiation and discussion to manage negative social influences.	Support from others identified as important and used for smoking reduction or cessation, and increasing PA.

Table 1 shows the intervention components, aims, content and respective process and outcome evaluation.

9.2 Support as usual

Participants allocated to both arms of the trial will receive guidance for smoking reduction and cessation, including web links to what is offered at local level, or paper versions of this information. In the current financial climate and without clear evidence of benefit and a clear pathway of care, it

is unlikely that there will be much support for smoking reduction as described as usual care. Given the rapidly changing public health environment we do not propose to request approval for this guidance or amendments from the REC if and when changes occur to what is offered locally to prevent unnecessary delays to the trial but will be happy to forward versions as appropriate.

10 Follow-up Assessments – all participants

10.1 3 month follow-up assessments

The 3 month assessments will be mailed to participants in the form of a questionnaire booklet, with a cover letter, and freepost return envelope. An opportunity will be given for participants to complete the questionnaire booklet over the telephone with a member of the local research team if they would prefer. A subset of study participants will also receive an accelerometer by post, and instruction sheet at the 3 month time point.

The 3 month questionnaire booklet contains questions relating to the following:

- Smoking behaviour
- Importance and confidence in smoking reduction and cessation
- Importance and confidence in being physically active
- Availability of support to reduce smoking and increase physical activity
- Use of physical activity for smoking regulation
- Self-reported physical activity (7-day physical activity recall)
- Planning to change smoking
- Planning to change physical activity
- Self-monitoring of smoking
- Self-monitoring of physical activity
- Urge & strength of urge to smoke
- Use of e-cigarettes and NRT (nicotine replacement therapy) products
- Health related quality of life (EQ-5D-5L & SF12)
- Physical activity (accelerometer) (7 days)
- Self-reported height and weight (BMI)
- Health service utilisation and costs, including smoking related costs
- Serious adverse event reporting

Participants who self-report that they have quit will be invited to attend a face-to-face assessment, which will include the following additional assessments:

- Self-reported prolonged abstinence (since last quit attempt, with date, if relevant)
- Expired carbon monoxide (CO) measurement

A shopping voucher will be mailed to all participants upon CTU receipt of the completed 3 month questionnaire booklet. No additional incentive will be provided for selected participants to return the accelerometer.

Expenses to attend the expired CO assessment session will also be provided.

10.2 9 month follow-up assessments

The 9 month assessments will be mailed to participants in the form of a questionnaire booklet, with a cover letter, and freepost return envelope. An opportunity will be given for participants to complete the questionnaire booklet over the telephone with a member of the local research team if they would prefer.

The 9 month questionnaire booklet contains questions relating to the following:

- Smoking behaviour
- Self-reported physical activity (7-day physical activity recall)
- Use of e-cigarettes and NRT (nicotine replacement therapy) products
- Health related quality of life (EQ-5D-5L & SF12)
- Self-reported height and weight (BMI)
- Health service utilisation and costs, including smoking related costs
- Serious adverse event reporting

Participants who self-report that they have quit will be invited to attend a face-to-face assessment which will include the following additional assessments:

- Self-reported prolonged abstinence (since last quit attempt, with date, if relevant)
- Expired carbon monoxide (CO) measurement

A shopping voucher will be mailed to participants upon CTU receipt of the completed 9 month questionnaire booklet.

Expenses to attend the expired CO assessment session will also be provided.

10.3 15 month follow-up assessments

The 15 month assessments will be mailed only to participants who are confirmed quitters at 9 months. The assessments will be in the form of a questionnaire booklet, with a cover letter, and freepost return envelope. An opportunity will be given for participants to complete the questionnaire booklet over the telephone with a member of the local research team if they would prefer.

The 15 month questionnaire booklet contains questions relating to the following:

- Smoking behaviour
- Use of e-cigarettes and NRT (nicotine replacement therapy) products

Only participants who have been confirmed as quitters at 9 months and self-reported quitting at 15 months will be invited to participate in the following 15 month assessments:

- Self-reported prolonged abstinence (since last quit attempt, with date, if relevant)
- Expired carbon monoxide (CO) measurement

A shopping voucher will be mailed to participants upon CTU receipt of the completed 15 month questionnaire booklet.

Expenses to attend the expired CO assessment session will also be provided.

10.4 Loss to follow-up

Based on the data from the TARS pilot study (EARS) [1] it is anticipated that 60-65% of TARS participants will complete follow-up at 3 months.

10.5 Expected duration of participation

From randomisation, participants will spend a maximum of 15 months in the TARS study, including follow-up assessments at 3, 9, and 15 months, depending on their self-reported smoking or abstinence status in the 9 month mailed questionnaire.

10.6 Schedule of delivery

	Screening & Baseline	Day 0	Intervention Week 1 – 8* (Intervention arm only)	Month 3	Month 9	Month 15
Eligibility check	X					
Consent	X					
Randomisation		X				
Demographics	X					
Importance and confidence in smoking reduction and cessation	X			X		
Importance and confidence in being physically active	X			X		
Availability of support to reduce smoking and increase physical activity	X			X		
Use of physical activity for smoking regulation	X			X		
Self-reported physical activity (7-day physical activity recall)	X			X	X	
Planning to change smoking	X			X		
Planning to change physical activity	X			X		
Self-monitoring of smoking	X			X		
Self-monitoring of physical activity	X			X		
Urge & strength of urge to smoke	X			X		
Use of e-cigarettes and NTR (nicotine replacement therapy) products	X			X	X	X
Health related quality of life (EQ-5D-5L & SF12)	X			X	X	
Self-reported weight & height (BMI)	X			X	X	
Health service utilisation and costs,	X			X	X	
Serious adverse events (self-reported)				X	X	
Self-reported prolonged abstinence (since quit attempt, with date, if relevant)				X	X	X
CO expired air confirmed abstinence (<10ppm)**				X	X	X
Accelerometer (7 days)				X		

*If a smoker wishes to quit at any time during the 8 week intervention period, they will be offered 6 weeks of additional support from the Health Trainer, a meeting with a specialist advisor in a stop smoking service, and pharmacological and behavioural support.

**Participants reporting prolonged abstinence from the point of quitting in the first 3 months of the study will be telephoned and invited to provide a sample of expired CO at a face-to-face visit with a site researcher. Participants with confirmed CO abstinence at 9 & 15 months will be contacted, and if continuing to report abstinence will be telephoned and invited to provide a sample of expired CO at a face-to-face visit with a site researcher.

10.7 End of trial

Participants who are self-reported quitters at 9 and 15 months will complete the study at the 15 month time point. All other participants will complete the study at the 9 month time point. The trial itself will end when all assessments that are expected to be conducted are completed.

11 INTERNAL PILOT

The first 4 months of the study will be part of an internal pilot, whereby the case for continuation of the study will be considered. Table 2 below shows the different scenarios for study progression.

Criteria	**Scenario 3**	**Scenario 2**	**Scenario 1**
% of internal pilot sample size target (240 smokers over 3 months) recruited across all sites.	<50%	50- 79%	⩾ 80%
Intervention engagement (% who have at least 1 session of the intervention).	<50%	50-79%	⩾ 80%
Proposed Action	No progression (see note 2 below)	Discuss with TSC and Funders about progression and resources needed to achieve target.	Proceed to full trial with an agreed plan to make up the shortfall.

Table 2 showing progression rules for stepping from internal pilot to full trial

NB. (1) Achievement of a single criteria but not the other requires discussion about progression.

(2) A figure of <50% for recruitment could only lead to progression if the internal pilot phase duration was extended due to especially encouraging recruitment or engagement in the latter part of the planned 4 month internal pilot window or one or more sites had delayed recruitment.

In addition to a review of recruitment and engagement at 12 months into the study, an assessment will be made in month 16 regarding the ability to follow-up participants at the 3 month assessment. The study may not progress if at least a 50% response rate at 3 months, is not reached. If recruitment is between 50-64%, progression of the study will depend upon discussions with the funder and the trial management groups. If the 65% recruitment target is met then the study will proceed, but with agreed plan for improvement.

12 WITHDRAWAL CRITERIA

A participant may, at any time, withdraw from the study without giving a reason, and without it affecting his/her clinical care. Participants will be asked to give a reason for withdrawal from the study but do not have to provide one. Participants who wish to withdraw will be given the option to continue with partial follow-up, e.g. provide primary outcome data only, to minimise data loss. Participants who withdraw from the study will not be replaced. The CTU data management team will ensure that participants who formally withdraw from the study are not contacted for any subsequent follow-up data collection (aside from any partial follow-up arrangements made with individual participants). Data collected prior to withdrawal will be included in the study analysis unless a participant specifically requests that their data are removed from the database. If a participant withdraws for the study they will not be replaced.

13 COMPLIANCE

Appointments will be arranged at times and places to suit the participant. Up to two reminder letters, and a follow-up phone call will be made to participants if they don't return the accelerometer. Up to two reminder letters will be issued to remind participants to return the questionnaire booklets, and the option of the participant telephoning a member of the research team to aid completion of the questionnaire booklets will be offered. A shopping voucher will be mailed to participants upon CTU receipt of the completed baseline, 3, 9 and 15 month questionnaire booklets. Motivational postcards may be mailed to participants ahead of the 3, 9 and 15 month follow-up assessments being sent out to increase response rates.

14 ETHICAL CONSIDERATIONS

14.1 Risks to participants

Moderate intensity physical activity is safe and is recommended for most adults. It is anticipated that most smokers will increase walking, and walking has no contraindications for most. Other physical activities will also be offered in the community, and participants will be advised on the suitability of these.

14.2 Protection against risks

During the screening process those smokers who are contraindicated for moderate intensity physical activity, or who have injury or illness which might be aggravated by exercise, will be required to gain approval from their GP before engaging in the study. Vigorous intensity activity can acutely and transiently increase the risk of sudden cardiac death and acute myocardial infarction in susceptible persons, so the focus of all recommendations for increasing PA will be on moderate intensity PA. Participants will be given clear guidance on exercising at this intensity (ie, something that increases the heart and breathing rate but not to the point of breathlessness or unable to maintain a conversation). Participants will be advised to seek approval from their GP prior to engaging in any vigorous intensity PA, regardless of age and gender. The smokers will be monitored for contraindications to exercise, for adverse events including physical symptoms (e.g. chest pain, extreme breathlessness), or change in health status at each counselling session.

All study personnel will be asked to comply with their employers lone working policy. All staff working with study participants will be required to complete Disclosure and Barring Service (DBS) checks, as they may be working with vulnerable individuals.

14.3 Potential benefits of the proposed research

The smokers participating in the study may have a greater chance of stopping smoking and remaining abstinent, relative to those who receive usual care. We may expect that those in the exercise intervention will have an enhanced opportunity of stopping smoking. Those who increase and maintain regular physical activity during and following the study will receive many general health benefits, including a reduced risk of developing cardiovascular disease, stroke, hypertension, obesity and some cancers, even if they continue smoking [60].

14.4 Importance of the study knowledge to be gained

Little is known about if and how behavioural support can help smokers to cut down, and if cutting down then leads to more quit attempts and continuous abstinence. If the physical activity intervention is shown to be effective and cost-effective for increasing quit attempts and smoking cessation it will offer important evidence for the design of behavioural interventions which are not currently available in the NHS. Smokers are typically less active than the general population, [58] and evidence from interventions that help change multiple health behaviours are urgently required. Weight gain is common among quitters [62, 38], but nothing is known about the effects of smoking reduction on weight gain or weight concern. This study may provide unique information on changes in a variety of psychological variables (eg, cravings and withdrawal symptoms) and weight gain and weight concerns among those who cut down and quit.

15 SAFETY REPORTING

15.1 Definitions:

15.1.1 Adverse event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs in study participants whether or not related to any research procedures or to the intervention.

15.1.2 Serious adverse Event (SAE)

A serious adverse event in the context of this study is any untoward medical occurrence that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalisation
- Results in persistent or significant disability/incapacity

When an AE occurs, the responsible investigator must assess whether the event is classified as serious (i.e. an SAE).

15.1.3 Reporting requirements for this study

The recording and reporting of non-serious AEs in this study is not required. SAEs will be reported from the time of consent until 4 months after the last trial intervention. If an unreported event from this time period is identified at a later date, retrospective reporting must occur immediately. Events occurring outside of this time period may still be reported if the Investigator feels that it is medically important. Information about SAEs may be captured in a variety of ways (see below). SAE report forms will be returned to the CTU, and entered into the study database. The Trial Office is responsible for reporting relevant events to the Sponsor, and ethics committee within required timelines in accordance with trial procedures and regulatory requirements. The PI is responsible for reporting events to local parties, in accordance with local practice. All reportable events and any others as advised by the main REC, will be sent to Investigators for submission to relevant parties in accordance with local practice. Trial staff will send a safety report to the main REC, and to the Sponsor annually. Sites should distribute this report in accordance with local practice and regulatory requirements.

15.2 Serious adverse event self- reporting at 3 and 9 months

The questions in the self-completion study questionnaire booklets ask participants to record the number of in-patient episodes within a set recall period. At the 3 and 9 month time points, participants are asked to record if they have been hospitalised, the reason for any hospital admission during the past three and six months respectively and whether they think that the hospitalisation was related to participation in this study. On receipt of a questionnaire indicating a past hospital admission, the CTU will liaise with the relevant local RA who will be responsible for ascertaining further details about the SAE from the participant and/or GP records as appropriate.

15.3 Notification of SAEs via GP

Once a participant is recruited to the study, the participant's GP will be notified by letter. The notification letter includes a request for the GP to contact the CTU in the event of the GP becoming aware of any SAE. On being informed of an SAE, the CTU will liaise with the relevant local RA who will be responsible for ascertaining further details about the SAE from the participant and/or GP records as appropriate.

15.4 Notification of SAEs from other sources

It is possible that the local research team or CTU may become aware of an SAE via patient or relative self-report or some other channel. In such cases, the local RA will be informed of the SAE in order to ascertain further details for reporting to the CTU.

15.5 Death/life threatening events

In the case of death or life-threatening events, on the day of becoming aware of the event, please telephone the Trial Office. The appropriate CRFs must be submitted in accordance with the CRF schedule. In the case of death, where possible, a copy of the death certificate and post-mortem report (if applicable) should be submitted to the Trial Office as soon as possible. Names and hospital numbers must not be visible on these documents. The participants trial number and initials must be clearly added to the document using black ball-point ink.

16 DATA MANAGEMENT

16.1 Data collection

Data will be recorded on study specific data collection forms (CRFs), by a suitably qualified individual cited on the site signature and delegation log. Participants will complete participant-reported outcome measures (PROMs). Data will be collected on paper for both study arms. All persons authorised to collect and record study data at each site will be listed on the study site delegation logs, signed by the relevant PI. Original versions of the CRF should be sent to CTU, and copies kept at site.

Trial staff will maintain regular communication with sites, through routine calls, mailings and/or meetings. In the event of persistent issues with the quality and/or quantity of data submitted, an on-site monitoring visit may be arranged. In such circumstances, patient notes and the investigator site file must be available during the visit. The representative from the Trial Office will work with the site staff to resolve issues, offer appropriate training if necessary, and determine the site's future

participation in the trial. An audit may be arranged at a site if the Trial Management Group feels it is appropriate. Audits will be conducted by an independent team, determined by the Trial Management Group. If a regulatory inspection is planned at a participating site, site staff should contact the Trial Office to discuss any action necessary.

16.2 Participant numbering

Each participant will be allocated a unique study number following randomisation, and will be identified in all study-related documentation by their study number and initials. A record of names, addresses, telephone numbers and email addresses linked to participants' study numbers will be stored securely on the study database for administrative purposes.

16.3 Source data

For the purposes of this study source data will include:

1. Patient's medical records, held by the NHS.

2. Patient self-reported outcome measures (PROMS) completed in the questionnaires at baseline, and the 3, 9 and 15 month follow-up assessments. Accessible by members of the CTU.

Source data will be made available for the purposes of on-site monitoring visits, audits, and regulatory inspections.

16.4 CRF completion

Each site will be provided with an Investigator Site File (ISF) containing Case Report Forms (CRFs). Data collected on each participant must be recorded by the local Principal Investigator, or designee, as accurately and completely as possible. The Principal Investigator is responsible for the timing, completeness, legibility, accuracy and signing of the CRFs, and he/she will retain a copy of each completed form. All fields MUST be completed. If a test or measurement was not done, please indicate why that was omitted on the CRF. Entries must be made in black ballpoint pen. Errors must be crossed out with a single line leaving the original data un-obscured (i.e. without overwriting), the correction inserted and the change initialled and dated. An explanatory note should be added if necessary. Correction fluid/tape/labels must not be used. All data submitted on CRFs must be verifiable in the source documentation. Any deviation from this must be explained appropriately.

Completed CRFs should be returned to:
TARS Study Office
Peninsula Clinical Trials Unit
Plymouth University Peninsula Schools of Medicine & Dentistry
N16, ITTC Building 1
Plymouth Science Park
Plymouth
PL6 8BX

16.5 Questionnaires

In order to determine if the intervention has an effect on reducing smoking, participants will be asked to complete a questionnaire booklet, at baseline, 3 months, 9 months and 15 months (if applicable). The baseline questionnaire booklet should be given to, or posted to participants after written consent is obtained but prior to study randomisation. Further questionnaire booklets will be posted to participants at the 3, 9 and 15 (if applicable) month time points. Completed questionnaire booklets should be returned to the CTU using the pre-paid envelopes provided.

16.6 Data handling and record keeping

Completed CRFs will be checked and signed at the collaborating University sites by a suitably qualified member of the research team before being sent to the CTU. Original CRF pages and questionnaires will be posted to the CTU at agreed timepoints with copies of the CRF retained at the relevant study site. Forms will be tracked using a web-based study management system. All data will be double-entered by the CTU on to a password-protected database. Double-entered data will be compared for discrepancies using a stored procedure and discrepant data will be verified using the original paper data sheets. Incomplete, incoherent, unreadable or other problem data in the CRF pages will be queried by the CTU with study site staff during data entry to ensure a complete and valid dataset. Questionnaire data will not be queried with participants. The CTU may complete further validation of data items, perform logical data checks and raise further data queries after data collection has been completed. The final export of anonymous data will be transferred to statisticians for analysis after all data cleaning duties have been performed by the CTU, this will usually be via email or a removable storage device. Identifiable information will not be exported from the study database as part of the final export.

Accelerometers will be received by the CTU and data will be downloaded and linked to participant ID numbers. Files will be checked before the accelerometers are recirculated. Files will be then further analysed with bespoke software to classify data into levels of physical activity intensity using accepted cut-points. Standard operating procedures will be applied to make a decision about dealing with missing data. Selected primary and secondary accelerometer derived outcomes will be merged into an individual participant data set, and securely stored as below.

Identifiable information will be omitted from the transcriptions of the process evaluation interviews.

16.7 Data confidentiality

The research team will ensure that participants' anonymity is maintained on all documents. Data will be collected and stored in accordance with the current legal and regulatory documentation.

Electronic study records will be stored in a SQL server database, stored on a restricted access, secure server maintained by Plymouth University. Data will be entered into the database via a bespoke web-based data entry system encrypted using SSL. Access to electronic data will be permission based, with access to identifiable information limited to those processing questionnaires and performing initial screening activities. Data entered onto the database will be backed up according to PenCTU SOPs.

Within the CTU, anonymised paper-based study data will be stored in locked filing cabinets within a locked office. Any paper-based participant related identifiable data will be stored separately from the

study data. Copies of study data retained at study sites will be securely stored for the duration of the study prior to archiving.

Identifiable information will be omitted from the transcriptions of the process evaluation interviews.

16.8 Access to data

The CTU data team will have access to the full dataset, including identifiable data. Site based researchers will have access to the dataset for participants from their site, including identifiable information, to perform screening activities. Other members of the study team and the CTU will have restricted access to anonymised study data. Access will be granted to the Sponsor and host institution on request, to permit study-related monitoring, audits and inspections. Access to the database will be overseen by the CTU data manager and trial manager.

16.9 Archiving

Following completion of data analysis and submission of the end of study report, the Sponsor will be responsible for archiving the study data and essential documentation in a secure location for a period of five years after the end of the trial. No trial-related records should be destroyed unless or until the Sponsor gives authorisation to do so.

17 STATISTICAL CONSIDERATIONS

17.1 Sample Size

Since the primary analysis is a comparison in each allocated group of the proportions of the primary binary outcome, the sample size is calculated for a two-sided Fisher exact test. An abstinence rate of 5% for the control group, and detectable effect of 6% (i.e: an increase from 5% to 11% due to the intervention) are conservative estimates consistent with those from the EARS pilot study and those reported from a systematic review of pharmacological interventions. The corresponding odds ratio for this effect is 2.35. Participants with missing outcome data will be assumed to be still smoking, and the number of participants in each allocated group are assumed to be in the ratio of 1:1. Under these conditions, according to Stata v14.2, the minimum number of participants required to detect an abstinence rate of 11% compared to that of 5% in the control group with a significance level of no more than 5% and power of at least 90% is exactly 900, above which a power in excess of 90% is maintained (Figure 1). The Stata code and the R code used to verify this calculation is found in Appendix 2.

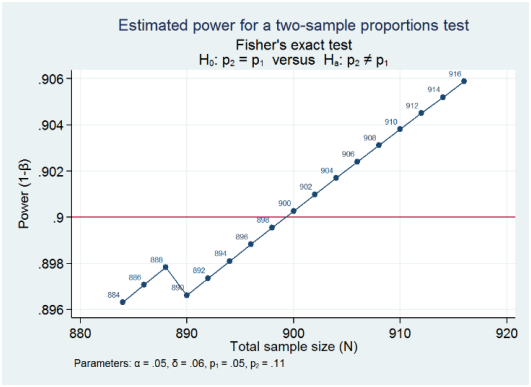


Figure 1: Plot of power of test afforded by each sample size ranging from 884 to 916, for equal group sizes and 5% significance level, where the proportion of CO-confirmed abstinence rates at 9 months is 0.05 and 0.11 in the control and intervention group, respectively.

17.2 Statistical analysis

The reporting and presentation of this trial will be in accordance with the appropriate CONSORT guidelines [79, 80] and in line with the Russell Standard schedule [6], with the primary comparative analysis being conducted on an intention-to-treat basis. All comparative analyses will allow for potential clustering by site and/or GP surgery and/or trainer, adjusting for important baseline covariates of socioeconomic status and recent quit attempts as well as the other stratification factor 2-item Heaviness of Smoking Index (HSI) [74]. Further exploratory analysis will also account for partial clustering in the intervention group by research staff within each site.

For completeness, unadjusted between-group comparisons will also be presented, based on chi-squared tests to compare binary outcomes (e.g. abstinence rates) and two sample t-tests to compare continuous outcomes (e.g. daily cigarette consumption) [74]. The between-group comparisons of smoking abstinence rates (and other secondary binary outcomes) will be expressed as odds ratios with 95% confidence intervals; the relative risk and corresponding confidence interval will also be presented as a more intuitive measure of the size of the intervention effect.

Where hypothesis tests are carried out, these will be at the 5% level for primary and secondary outcomes, and the 1% level for interaction terms. No adjustment for multiple analyses will be made; such adjustment methods are too conservative when outcomes are positively correlated, as they would be in this trial.

17.2.1 Baseline characteristics

Baseline characteristics of participants will be summarised, with descriptive statistics used to assess any marked baseline differences in demographics or outcome measures between the two allocated groups. Loss to follow-up after randomisation will be reported separate for each allocated group, and baseline characteristics examined to assess for potential bias.

17.2.2 Primary analysis of primary outcome

The primary analysis will be a logistic comparison of the primary outcome of CO-confirmed abstinence at 3 and 9 months post-baseline, using a mixed-effects model to account for clustering by site, with the adjustment for the HSI stratification factor, as well as important baseline covariates (i.e. age, gender, socio-economic status, level of smoking, recent quit attempts. Interpretation of the

primary effectiveness will be based on the adjusted odds ratio from this model, and the point estimates reported with 95% confidence intervals. Those participants with missing outcome data will be assumed to be still smoking [6].

17.2.3 Secondary analysis of primary outcome

Although the trial is not powered to detect the influence of moderating factors on the primary or secondary outcomes, secondary analyses will be undertaken to explore whether the intervention effect is modified by sociodemographic and/or behavioural factors (e.g. age, gender, socio-economic status, baseline HSI, MVPA level, and confidence to quit). These analyses will be undertaken for the primary outcome and for the reduction in smoking (both the actual reduction and the proportion of participants reporting $\geqslant$50% reduction in smoking level). The multi-variable models outlined above will be extended to include the interaction term of allocated group and the potential modifying variable, tested at the 1% significance level. However, such analyses will have low statistical power and likely to yield false positive findings, so the results will need to be conservatively interpreted. We will also conduct a sensitivity analysis to determine if the intervention dose actually received influenced differences in outcomes.

17.2.4 Analysis of secondary outcomes

Between-group comparisons will be undertaken at 3 and 9 months post baseline for all available outcome measures, and only prolonged abstinence rates at 15 months. Analysis will use multi-variable logistic regression to compare these secondary outcomes between allocated groups, with adjustment for the stratification factors [site, HSI], as well as important baseline covariates (i.e. age, gender, socio-economic status, level of smoking, recent quit attempts).

The between-group comparisons of continuous outcomes (e.g. daily cigarettes smoked, minutes of MVPA) will be reported as mean differences together with 95% confidence intervals, unless the outcomes are substantially skewed. Multi-variable linear regression will be used to compare continuous variables between allocated groups, with adjustment for the stratification factors, important baseline covariates, and baseline outcome values, where relevant.

Sensitivity analysis will examine the potential influence of participants lost to follow-up under varying assumptions. Further sensitivity analysis may be undertaken if any marked imbalance between allocated groups is seen in important baseline characteristics, by further adjustment for such baseline characteristics in the multi-variable models detailed above.

Finally, we will conduct exploratory mediational analysis to determine if any effect of trial arm on the primary outcome was mediated by changes in smoking, physical activity, from baseline to 3 months. We will also examine if changes in smoking and physical activity are mediated by changes in various secondary outcomes (eg, importance and confidence to reduce smoking/increase physical activity; self-monitoring and goal setting; cravings)

17.2.5 Termination of the trial

Based on recruitment rates from the EARS pilot study, it is estimated that 20 smokers a month can be recruited for 12 months from each of the four recruitment sites. However an interim analysis of the recruitment rate is planned at the end of the internal pilot-trial phase at four months after the start of the study. Progression will be decided according to the scenarios set out in Table 2, Section 11. Achievement of a single criterion, but not the other, requires discussion about progression. A figure of <50% for recruitment could only lead to progression if the internal pilot phase duration was

extended due to especially encouraging recruitment or engagement in the latter part of the planned 4 month internal pilot window. Results from the process evaluation will help inform decisions regarding progression, where further discussion is required, as well as any changes needed to address a shortfall in the number of recruited participants.

In addition to a review of recruitment and engagement at 12 months, the follow-up rate at the 3 month assessment will also be assessed. We propose no progression if we don't achieve at least a 50% response rate at 3 months, discussion about progression if between 50-64% and automatic progression (with agreed plans to improve it) if we achieve at least a 65% response rate.

A futility analysis is planned nine months after the 12-month recruitment phase ends. This analysis will assess for a difference in the primary outcome between allocated groups, that is: the proportions of participants achieving CO verified prolonged abstinence at 3 and 9 months post baseline. If there is evidence of a statistically significant difference ($p<0.05$) between allocated groups, then the trial will continue and all participants abstinent at nine months will be followed-up again at 15 months post baseline, and the total trial duration will be 44 months. If there is insufficient evidence of a significant intervention effect at 9 months, then the 15 month follow-up will be abandoned and the trial duration will be 39 months, with a corresponding saving in resources.

18 PROCESS EVALUATION

The process evaluation is presented in two parts: (1) the internal pilot, focussing on trial methods, specifically recruitment, as well as early engagement in and implementation of the intervention and (2) the main trial, which focusses on understanding of if and how physical activity, alongside other smoking reduction strategies, contributes to smoking reduction and cessation.

A mixed-methods embedded process evaluation will enable us to more fully understand how the respective components of the intervention are interacting and featuring if and when smokers do manage to reduce and quit smoking. It is important to understand not only if the intervention is effective but also whether there are some key and not so important components to improve more efficient training and delivery during any implementation phase. Equally, if the intervention is shown not to be effective then it is important to understand why and whether future intervention modifications are merited. Given the sparsity of rigorous research on behavioural approaches such as the one proposed for the target population it will be important to maximise what can be learnt. Further, it is vital, in the initial internal pilot phase, for the process evaluation to focus on understanding and refining the trial methods in order to maximise recruitment, and initial intervention engagement.

18.1 Internal pilot:

During the internal pilot phase (1-4 months of recruitment) the focus will be on feasibility and acceptability of trial methods and early understanding of aspects of intervention implementation including training and supervision, as well as early indications of intervention engagement, as follows:

18.1.1 Interviews with decliners:

To inform our understanding of recruitment feasibility and acceptability, participants who are eligible but who decline to join the study will be asked to indicate by return of the reply slip included in the TIP if they are willing to be contacted for a short telephone interview to determine what influenced their decision not to join the study. Questions will broadly focus on the following: (a) understanding of what the study/intervention is about based on the TIP materials; (b) barriers to taking part in the

study; (c) perceptions of materials contained in the TIP; (d) perceptions of what would influence them to take part in the study.

18.1.2 Interviews with study participants:

To further inform our understanding of the acceptability and feasibility of both recruitment and intervention we will interview (either in person or by phone) study participants from both the control group and intervention group. Questions will broadly focus on the following: (a) understanding of what the study/intervention is about based on the TIP materials; (b) motivation for taking part in the study; (c) perceptions of materials contained in the TIP; (d) perceptions of being informed of their allocation to the control group and intervention group (as applicable). Interviews with participants in the intervention group (both those who have engaged with the intervention and those who have not engaged with the intervention within 3 weeks of being informed of their allocation), will also inform our understanding of perceptions of engaging with the intervention. Questions will be based on issues including (a) initial engagement; (b) acceptability of core components of the intervention; (c) acceptability of materials; (d) use of other aids to self-regulate smoking.

We will seek to interview as many participants as possible at this stage but anticipate that decliners may also be not willing to be interviewed.

18.1.3 Interviews with Research Assistants:

Short telephone/Skype interviews will be conducted with Research Assistants (RAs) at each site in order to identify barriers and facilitators to recruitment. Interviews will be recorded and summary notes taken. RAs will be asked to keep a log of their recruitment observations to support their participation in regular interviews (approximately every 2-3 weeks in the pilot phase), the findings of which will be formatively fed back to each site in order to trouble shoot teething issues and maximise recruitment.

18.1.4 Interviews with Health Trainers:

Health Trainers (HTs) will be interviewed (via telephone/Skype/in person as appropriate) at key points both immediately prior to and during intervention delivery in the pilot phase. HTs will be interviewed at each site in order to inform our understanding of (a) perceptions of acceptability and utility of HT training and manual; (b) receipt of training objectives (training fidelity); (c) perceptions of supervision; (d) experience of participant allocation; (e) perceptions of experience of delivering the intervention delivery including both practical issues and delivery of core competencies. Issues raised will be fed formatively into supervision and training updates as appropriate.

18.1.5 Interviews with GPs/Practice managers:

In addition to notes kept by the Research Assistants, GP practice staff involved in pre-screening at each site will be invited to take part in short telephone interviews to inform our understanding of this process. Interviews will broadly focus on: (a) acceptability and feasibility of use of read codes used as proxy indicators for inclusion/exclusion criteria; (b) resource needed/burden on practices; (c) barriers and facilitators to effective pre-screening and working with the research team. Interviews will be conducted most intensely in the initial stages of screening and recruitment and findings used to enhance the acceptability and effectiveness of screening methods.

Due to a limited budget awarded for the process evaluation, although we will audio record all interviews conducted during the process evaluation during the internal pilot, not all interviews will be transcribed during the internal pilot. Where interviews are not fully transcribed, detailed notes will be kept and collated to inform decisions about progress to the full trial.

18.2 Main trial

We will use recorded data from focus groups (one per site) and semi-structured interviews with HTs (n=8) and participants (n=20). Participant interviews will be conducted either in person or via telephone, with participants purposively selected by site. Field notes from HT training and supervision, HT session contact notes, and from recorded intervention sessions will also form the data corpus. For the latter, intervention fidelity will be assessed using a coding system developed during the pilot study which appeared to be robust in its application for assessing the delivery of the key intervention processes [63]. Recorded sessions through the multiple sessions (3 sessions from 30 participants, i.e. 90 session recordings held between a single HT and participant will be assessed to ensure capture of variations in planned intervention content over time. Participants will be selected where recordings have been achieved at the start, middle and end of engagement, and will be purposively sampled by outcome (e.g. those who have made a quit attempt; reduced smoking) and demographic characteristics (e.g. age and gender). Health Trainer contact notes and records of contact number, type and duration will further inform the picture of intervention engagement.

The potential use of smoking reduction and cessation aids by participants in the TARS study is somewhat of an unknown, and will need to be assessed during initial intervention refinement (as above) and within the trial, particularly in terms of the impact on how physical activity plays a role in smoking reduction and possibly cessation. Also, with enhanced training of HTs they may be better equipped to support physical activity change as a way to aid smoking reduction and cessation (based on possible ways this could work identified above), but equally there may still be a proportion of smokers who find alternative approaches to reduction to be more acceptable. Semi structured interviews will be conducted with participants purposively sampled to cover a range of demographics and outcomes. It is intended to identify participants who have and have not engaged in physical activity, and those who have and have not reduced smoking to provide additional rich information about perceptions of delivery and receipt of the intervention. Key intervention components which facilitated intervention effectiveness (or not) will be analysed to complement other information in support of our logic model or not. Further, participants' understanding and experience of the intervention received will be explored (receipt fidelity). PPI groups will be consulted to help us understand this information and translate it into dissemination and implementation plans as appropriate.

18.3 Analysis

Qualitative data will be subject to thematic analysis using constant comparison techniques to extract concepts and themes [76] (and using NVivo to manage the data). The transcripts relating to smoker experiences of the intervention will also be analysed to produce a sample of individual narratives, allowing an increased insight into the processes of intervention engagement and the processes of supporting behaviour change [77]. Second coding of a sample of the transcripts and discussion of the emerging coding framework, as well as techniques such as negative case-finding and hypothesis testing will be used to increase the depth of analysis and enhance the likely objectivity of interpretation [79].

As reported in the section above on secondary outcomes, we will examine changes in smoking and physical activity and related beliefs, as well as information about intervention engagement. We will conduct exploratory mediation analysis to determine if changes between baseline and 3 months in items to assess behaviour change constructs (ie, perceived importance and confidence to change smoking and physical activity, availability of support, use of physical activity to aid changes in smoking, urges and strength of urges to smoke, and self-monitoring and engagement in planning to change smoking and physical activity) mediate changes in smoking and physical activity.

19 ECONOMIC EVALUATION (Cost-Effectiveness Analyses)

19.1 Health economic outcome measures

Health related quality of life (EQ-5D-5L)

The EQ-5D is a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group, 1990). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels; no problems, slight problems, moderate problems, severe problems, and extreme problems (Herdman et al 2011 [69]). In this study participants will be asked to complete EQ-5D-5L as part of the questionnaire booklet mailed to them from CTU at baseline, and then at 3 months follow-up and 9 months follow-up.

Health service utilisation and costs (including smoking related costs)

A resource use questionnaire (RUQ) has been developed and used to collect self-report data from participants on key areas of health care resource use (e.g. GP contacts, hospital admission). The RUQ is based on previously used questionnaires of this type in a primary care research setting. Participants will be asked to complete this as part of the questionnaire booklets at baseline, 3 and 9 months. The booklet will be mailed to participants from CTU at 3 and 9 months.

19.2 Economic evaluation

An economic evaluation will be undertaken to estimate the cost-effectiveness of the intervention versus SAU, for smokers wishing to reduce but not quit smoking, alongside the RCT (trial-based analyses, over 9 month follow up) and over a longer term time horizon using a decision analytic model based framework. The primary perspective of the analyses will be that of the NHS and Personal Social Services (i.e. Third Party Payer), with a broader perspective explored in sensitivity analyses; results will be presented in a UK policy-relevant context. The primary economic endpoint will be the QALY, derived in trial-based analyses using the EQ-5D-5L, over the 9-month follow-up, with cost-effectiveness presented using incremental cost per QALY.

In the prior pilot study (EARS) methods of data collection on resource use associated with the delivery of the intervention were developed and tested. These methods will be used (including some adaptation where appropriate) in this full RCT and evaluation, to collect data on the delivery of the TARS intervention (HT time inputs for delivery of the intervention, and resources related to training and supervision of HTs, plus consumables). Data on time input for HTs (contact time, participant related non-contact time) will be collected within-trial using a HT 'contact sheet' completed by HTs for each contact with intervention participants. Data will be collected within-trial, via Trial Coordinator/s, on resource use for the training of HTs, and for ongoing specific supervision requirements for HTs, plus other related consumables and intervention expenses. A resource use questionnaire (RUQ) will be used to collect self-report participant data on use of health care services. As above, this RUQ will be completed at baseline, 3-month and 9-month follow-up assessments, and will be used to derive a profile of resource use at participant level over the 9-month follow-up. Items of resource use will be combined with published estimates of unit costs (e.g. NHS reference costs, data from PSSRU [66]), to estimate costs associated with delivery of the intervention in a future policy relevant setting, and to estimate the costs associated with broader service use by group.

The economic endpoint will be the QALY, and the EQ-5D-5L data from trial participants will be used to derive health state values at each time point, using the published tariff values for England (presently recommendations are for values to be derived using methods reported by Van Hout et al 2015 [81]). The EQ-5D-5L data will be used to derive participant level QALY data over the 9-month follow up, using the area under the curve approach (Brazier et al, 2007 [73]).

A trial-based cost-effectiveness analysis will present estimates of intervention cost, broader resource use costs, and QALYs, by group, and will estimate the incremental cost per unit of outcome (e.g. cost per incremental QALY) over the 9-month follow-up. Analyses will assess uncertainty, and will present sensitivity analyses. Analysis of cost data, for health care services will be undertaken using regression based analyses to estimate differences between groups over time, adjusting for baseline cost estimates, and other co variates specficied in the analyses of effectiveness, and through applying bootstrap methods to account for the non parametric nature of cost data. A similar regression based approach will be used to estimate differences in EQ-5D-5L values and derived QALYs between intervention and control participants.

In addition to the trial-based economic evaluation, a model-based economic evaluation will also be undertaken to estimate the cost effectiveness of the intervention versus SAU. This will adopt a longer term perspective (lifetime horizon/time-frame), beyond the trial follow, to present a policy relevant cost effectiveness analyses, consistent with the approach commonly applied in smoking cessation settings. A decision-analytic model will be used to deliver this model-based evaluation, and to allow the evidence synthesis required to perform this analysis. A decision analytic model was developed and used as part of the prior pilot study (EARS), and that model will be used as the basis for the model-based evaluation in the current TARS project. However, we will update the review of the literature (undertaken in the pilot study) and we will further develop and adapt the model developed where required and appropriate.

Building on our prior research on model development, we will update to previously reported review of the literature to identify new research on methods related to modelling cost effectiveness in a smoking cessation setting, and on important input parameters for a model based framework (e.g. relapse rate, mortality data). The starting point for modelling cost effectiveness is effectiveness (trial) data on abstinence rates (intervention vs SAU). Thereafter, through evidence synthesis, the model will predict smoking status over time and will be driven by estimates of mortality by smoking status. Using a Markov type model, with states for ‘smoker’, ‘former smoker’ and death, and a cohort simulation model structure (although other scenarios will be considered), aligned to age (e.g. decile age bands) and gender, we will estimate the number of long term quitters, the cost per life year saved, and cost per QALY gained. In the pilot study (EARS) we used an exponential survival function for remaining smoke free (time to event/relapse analyses), over an initial 7-year period of follow-up (beyond initial 12-months), consistent with evidence that the proportion of quitters follows a decreasing trend. Prior research did not include spontaneous quit rate beyond 8 years, but this will be explored in current (TARS) model development (e.g. using data from Coleman et al [67]). The TARS study will we expect allow development of a the model in terms of mortality by applying mortality rates dependent on time since quit to model the relation between sustained abstinence and smoking related mortality. Detail on this is presented in the pilot study report (Taylor et al, 2014, Chapter 6 [1]). In prior research we have applied mortality data with data on health state values (QALY weights) by smoking status, available by age and gender [68]. TARS will build on prior research on the modelling of the impacts of smoking cessation strategies, to provide a rigorous presentation of estimates of the cost effectiveness of the intervention applied in the research proposed here. Methods will include cost analyses, literature review, evidence synthesis, trial-based

cost effectiveness analyses (CEA), and longer term CEA using a decision-analytic modelling framework. The TARS study will apply methods of good practice in decision analytic modelling in a HTA context, and will explore uncertainty in assumptions and data inputs in a thorough and transparent way, including scenario analyses, one-way and multi-way sensitivity analyses and using probabilistic sensitivity analyses (alongside model based analyses).

20 DATA MONITORING

The CTU trial manager and data manager will devise a risk-based monitoring plan specific to the study which will include both central monitoring strategies and study site visits (usually by the trial manager) as appropriate. The monitoring plan will be agreed by the Sponsor and PMG and reviewed periodically in line with updated risk assessments. The risk assessment and monitoring plan are active documents and will remain subject to change throughout the study.

Data will be monitored centrally for quality and completeness by the CTU and every effort will be made to recover data from incomplete pages. The CTU data manager will oversee data entry and initiate processes to resolve data queries where necessary.

All study procedures will be conducted in compliance with the protocol and according to the principles of Good Clinical Practice (GCP). Procedures specifically undertaken by the CTU team (e.g. data management, trial management and study monitoring) will be conducted in accordance with CTU SOPs. The PIs and the participating NHS Trusts will be required to permit the CTU trial manager or deputy to undertake study ‐ related monitoring to ensure compliance with the approved study protocol and applicable SOPs, providing direct access to source data and documents as requested.

20.1 Data monitoring plan

A risk based trial monitoring plan will be developed and agreed by the Sponsor and PMG. This will involve central data monitoring but may also include on-site monitoring by the CTU trial manager. The Principal Investigators will be required to permit the CTU trial manager or deputy to undertake such monitoring as required to ensure compliance with the approved trial protocol and applicable SOPs, providing direct access to source data and documents as requested.

20.2 Quality assurance

The CI will be responsible for the overall running of the trial and for the local conduct of the trial at the Plymouth site. The CTU will coordinate trial-related activities and assist with overall trial management, monitoring and production of progress reports. The CTU will also organise the web-based randomisation, prepare the database, provide double data entry into the database, and oversee safety reporting activities.

The Chief Investigator for the trial is Professor Adrian Taylor. The trial will be co-ordinated from the Trial Office at Peninsula Clinical Trials Unit (PenCTU). The Trial Office will be responsible for ethical submissions, study site coordination (including training and accreditation), document design and production, monitoring trial procedures, trial meeting organisation, data queries, data monitoring, randomising participants, and safety reporting. Statistical analysis, database cleaning and the writing of the final study report will be performed by statisticians at PenCTU.

Prior to activating a site to recruitment, it is necessary for all staff members working on the trial to participate in an induction session. An accreditation checklist will be completed for all sites to confirm that pre-activation activities have been completed and all relevant staff members are able to participate. Support will be offered to staff at participating sites to ensure they remain fully aware of trial procedures and requirements. Additional support and training will be offered to sites as appropriate where necessary (e.g. if the recruitment rate is lower than expected).

A Trial Master File (TMF) will be set up and held securely at the CTU, in accordance with CTU SOPs. CTU will produce and provide each Investigator Site with an Investigator Site File. Any updates to essential trial documentation will be circulated to all participating sites – it is the responsibility of the site to update their Investigator Site File as necessary.

20.3 Project Management Group (PMG)

The PMG includes a multidisciplinary team of clinicians and researchers who have considerable expertise in all aspects of trial design, conduct, analysis and quality assurance.

20.4 Trial Steering Committee (TSC)

The TSC will have an independent chairperson. Meetings will be held at regular intervals. The Trial Steering Committee, in the development of this protocol and throughout the trial, will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the IDSMC
- Informing and advising on all aspects of the trial

20.5 Data Monitoring Committee (DMC)

An independent data and safety monitoring committee will be established for this trial. Their main objective will be to advise the Trial Steering Committee as to whether there is evidence or reason why the trial should be amended or terminated based on recruitment rates, compliance, safety or efficacy. Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC. Members of the DMC will accept and sign the DMC Charter. This will include a declaration that they will maintain confidentiality and that they have no conflicts of interest. The trial statistical analysis plan will be agreed with the DMC.

20.6 Patient public involvement (PPI)

The TARS research team has worked with smokers, not as research participants, individually and in groups from across all communities, to guide research questions, study design and conduct, intervention development and dissemination over the past 15 years. For example, in 2007-9, Taylor spent many hours in NHS stop smoking clinics observing and discussing how physical activity could be valued and promoted as an aid to quitting, managing cravings and weight. Smokers in clinics helped us to identify the need to consider physical activity to reduce smoking for those not ready to quit. Many hours have been spent discussing with smokers how to support them to both reduce cigarettes and increase physical activity in a useful way. This experience led to various iterations and eventually the intervention delivered in our pilot exercise assisted smoking reduction (EARS) trial. PPI representatives also helped design the trial methods including the best ways to recruit participants, and patient facing materials. The TARS study has involved a University staff PPI group

of current and former smokers, and also smokers within 'peer researcher' groups (males and female) as part of an ongoing trial involving research staff to support multiple behaviour change in offenders in community supervision, to discuss and review the proposed methods and intervention and the implications of use of e-cigarettes and NRT. They had different views on the merits of e-cigarettes and NRT to reduce smoking and how various forms of physical activity may help, which will explored further in PPI meetings in the set-up phase of the proposed study. A university employee and non-employee PPI group (of former/current smokers) will meet monthly to input into intervention development as well as involve them in all aspects of developing and conducting the trial (costed at £6k). A selected group will contribute to project management group meetings and Trial Steering Committee meetings throughout the trial. They will also eventually help to interpret the findings in a dissemination workshop (costed at £3k) for key stakeholders, and help to maximise implementation opportunities if warranted. In our PPI plans it will be necessary to identify community champions who can promote the study across the sites, and seek to work with leading charities and organisations who support initiatives to reduce harm from smoking. Since the EARS pilot study the study team have also engaged with key stakeholders involved in commissioning and delivering research type community interventions outside of Stop Smoking Services, to assess where the proposed intervention would best fit and its perceived value, and the study team will continue to do this prior to and during intervention development.

21 ETHICS APPROVALS

The study will be undertaken subject to appropriate Research Ethics Committee (REC) approval and HRA (Health Research Authority) approvals. The trial will be conducted in accordance with the protocol, the principles of the Declaration of Helsinki and GCP. Any amendments of the protocol will be submitted to the Sponsor, HRA, and REC for approval. Substantial amendments that require review by REC and HRA will not be implemented until the REC and HRA grants a favourable opinion. All correspondence with the REC and HRA will be retained in the Trial Master File and Investigator Site Files. An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the original favourable opinion was given, and annually until the trial is declared ended. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC and HRA.

21.1 Protocol compliance

Protocol deviations will be monitored by the CTU and reported to the Chief Investigator and Sponsor as appropriate. Significant deviations from the protocol which frequently recur are not acceptable and may potentially be classified as a "serious breach".

21.2 Notification of serious breaches of GCP and/or the protocol

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to effect to a significant degree –

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial

The Sponsor will be notified immediately of any case where the above definition applies during the trial period. The Sponsor is responsible for notifying the REC of a serious breach in any study within seven days of the matter coming to their attention.

22 STATEMENTS OF INDEMNITY

This is an NHS-sponsored research trial. If an individual suffers negligent harm as a result of participating in the trial, NHS indemnity covers NHS staff and those people responsible for conducting the trial who have honorary contracts with the relevant NHS Trust. In the case of non-negligent harm, the NHS is unable to agree in advance to pay compensation, but an ex-gratia payment may be considered in the event of a claim. Any harm to participants arising from the design or management of the research is covered by the NHS Litigation Authority. There are no arrangements for the Sponsor to pay compensation in the event of harm to research participants where no legal liability arises.

23 PUBLICATION POLICY

The research team will work with stakeholders at each site, and nationally, to help to interpret the results and the implications for policy and practice. Dissemination may involve presentation at meetings of relevant support groups or other lay audiences, as well as NHS strategy forum at local and national level.

There will be a standing item on the agenda for each Project Management Group meeting on the publication plan and establishing authorship rules. It is expected that the trial protocol will be submitted for publication no later than the end of the 4 month internal pilot phase of the study. Reports will comply with current CONSORT guidelines for publishing randomised trials. The study results will be submitted for publication in relevant international, high impact, peer reviewed journals. Names of key collaborators and groups who have contributed to the trial will be clearly stated in all publications. The study findings will be presented at regional, national and international meetings as appropriate.

An invitation will be extended to the PPI group members to comment on the findings at a dissemination event, and work with other key stakeholders (ie, public health and lead professionals, commissioners of SSS and health promotion support) to maximise impact (eg, through policy changes such as revisions to NICE guidelines for smoking harm reduction).

24 STUDY ORGANISATIONAL STRUCTURE

The study will involve collaborative University sites at Plymouth, Nottingham, Oxford and South London, where research staff will be based, alongside the Principle Investigator. Recruiting sites, including GP surgeries and the community, will be chosen at each of the collaborative sites.

25 FINANCE

The TARS study is being funded by an NIHR HTA grant (reference number 15/111/01). The contract is between the NIHR and Plymouth Hospital NHS Trust (PHNT). PHNT have established collaborative agreements with each partner University, and Plymouth City Council. Excess Treatment Costs have been provided by Plymouth City Council and Public Health England.

26 REFERENCES

1. Taylor AH, Thompson TP, Greaves CJ, et al (2014) A pilot randomised trial to assess the methods and procedures for evaluating the clinical effectiveness and cost-effectiveness of Exercise Assisted Reduction then Stop (EARS) among disadvantaged smokers. Health Technol Assess 18:1–324

2. Thompson TP, Greaves CJ, Ayres R, et al (2015) An Exploratory Analysis of the Smoking and Physical Activity Outcomes From a Pilot Randomized Controlled Trial of an Exercise Assisted Reduction to Stop Smoking Intervention in Disadvantaged Groups. Nicotine Tob Res. doi: 10.1093/ntr/ntv099

3. National Institute for Health and Care Excellence (2013) Tobacco: harm-reduction approaches to smoking. NICE PH Guidance 45, London

4. Ussher MH, Taylor AH, Faulkner GEJ (2014) Exercise interventions for smoking cessation. Cochrane database Syst Rev 8:CD002295

5. National Institute for Health and Care Excellence (2008) Smoking Cessation Services. NICE PH Guidance 10, London

6. West R, Hajek P, Stead L, Stapleton J (2005) Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction 100:299–303

7. Buck D, Frosini F (2012) Clustering of unhealthy behaviours over time: Implications for policy and practice.

8. ASH (2015) The Economics of Tobacco: The ASH Factsheet. http://www.ash.org.uk/files/documents/ASH_121.pdf Downloaded 11/1/2016.

9. West R, Brown J (2015) Smoking in England 2007-2014.

10. Ferguson J, Bauld L, Chesterman J, Judge K (2005) The English smoking treatment services: one-year outcomes. Addiction 100 Suppl :59–69

11. McEwen A, Hajek P, McRobbie H, West R (2006) Manual of smoking cessation: A guide for counsellors and practitioners. Blackwell Publishing, Oxford

12. Beard E, Bruguera C, McNeill A, Brown J, West R (2015) Association of amount and duration of NRT use in smokers with cigarette consumption and motivation to stop smoking: a national survey of smokers in England. Addict Behav 40:33–8

13. Shiffman S, Hughes JR, Ferguson SG, Pillitteri JL, Gitchell JG, Burton SL (2007) Smokers' interest in using nicotine replacement to aid smoking reduction. Nicotine Tob Res 9:1177–1182

14. Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D (2008) "Cut down to quit" with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis. Heal Technol Assess 12:iii–iv, ix–xi, 1–135

15. Asfar T, Ebbert JO, Klesges RC, Relyea GE (2011) Do smoking reduction interventions promote cessation in smokers not ready to quit? Addict Behav 36:764–8

16. McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P (2014) Electronic cigarettes for smoking cessation and reduction. Cochrane database Syst Rev 12:CD010216

17. Brose LS, Hitchman SC, Brown J, West R, McNeill A (2015) Is the use of electronic cigarettes while smoking associated with smoking cessation attempts, cessation and reduced cigarette consumption? A survey with a 1-year follow-up. Addiction 110:1160–1168

18. Hitchman SC, Brose LS, Brown J, Robson D, McNeill A (2015) Associations Between E-Cigarette Type, Frequency of Use, and Quitting Smoking: Findings From a Longitudinal Online Panel Survey in Great Britain. Nicotine Tob Res 17:1187–94

19. Carpenter MJ, Hughes JR, Gray KM, Wahlquist AE, Saladin ME, Alberg AJ (2011) Nicotine therapy sampling to induce quit attempts among smokers unmotivated to quit: a randomized clinical trial. Arch Intern Med 171:1901–7

20. West R, Beard E, Brown J Smoking Toolkit Study. www.smokinginengland.info/latest-statistics. Accessed 1 Jan 2016

21. Brown J, West R, Beard E, Michie S, Shahab L, McNeill A (2014) Prevalence and characteristics of ecigarette users in Great Britain: Findings from a general population survey of smokers. Addict Behav 39:1120–5

22. Tan ASL, Bigman C a. (2014) E-cigarette awareness and perceived harmfulness: Prevalence and associations with smoking-cessation outcomes. Am J Prev Med 47:141–149

23. Kiviniemi MT, Kozlowski LT (2015) Deficiencies in public understanding about tobacco harm reduction: results from a United States national survey. Harm Reduct J 12:21

24. McNeil A, Brose LS, Calder R, Hitchman SC, Hajek P, McRobbie H (2015) E-cigarettes: An evidence update. London

25. Taylor G, Taylor A, Munafo MR, McNeill A, Aveyard P (2015) Does smoking reduction worsen mental health? A comparison of two observational approaches. BMJ Open 5:e007812

26. St Helen G, Havel C, Dempsey D, Jacob P, Benowitz NL (2015) Nicotine delivery, retention, and pharmacokinetics from various electronic cigarettes. Addiction. doi: 10.1111/add.13183

27. Haasova M, Warren FC, Ussher M, Janse Van Rensburg K, Faulkner G, Cropley M, Byron-Daniel J, Everson-Hock ES, Oh H, Taylor AH (2013) The acute effects of physical activity on cigarette cravings: systematic review and meta-analysis with individual participant data. Addiction 108:26–37

28. Taylor A, Katomeri M (2007) Walking reduces cue-elicited cigarette cravings and withdrawal symptoms, and delays ad libitum smoking. Nicotine Tob Res 9:1183–1190

29. Katomeri M, Taylor AH (2006) Effects of walking on desire to smoke and withdrawal symptoms during a smoking cue, and ad libitum smoking. Abstr. Eur Coll Sp Sci Conf

30. Reeser KA (1983) Unpublished Masters Thesis. University of Alberta, Canada

31. Thayer RE, Peters DP, Takahashi PJ, Birkhead-Flight AM (1993) Mood and behavior (smoking and sugar snacking) following moderate exercise: A partial test of self-regulation theory. Pers Individ Dif 14:97–104

32. Janse Van Rensburg K, Taylor A, Hodgson T, Benattayallah A (2009) Acute exercise modulates cigarette cravings and brain activation in response to smoking-related images: an fMRI study. Psychopharmacol 203:589–598

33. Janse Van Rensburg K, Taylor AH, Hodgson T (2009) The effects of acute exercise on attentional biases to smoking-related stimuli during temporary abstinence from smoking. Abstr. SRNT Conf.

34. Smith MA, Lynch WJ (2013) The neurobiology of exercise and drug-seeking behaviour. In: Ekkekkakis P (ed) Routledge Handb. Phys. Act. Ment. Heal. Routledge, New York, pp 478–489

35. Meeusen R, Piacentini MF, De Meirleir K (2001) Brain microdialysis in exercise research. Sports Med 31:965–983

36. Wang GJ, Volkow ND, Fowler JS, Franceschi D, Logan J, Pappas NR, Wong CT, Netusil N (2000) PET studies of the effects of aerobic exercise on human striatal dopamine release. J Nucl Med 41:1352–1356

37. Moraes H, Ferreira C, Deslandes A, Cagy M, Pompeu F, Ribeiro P, Piedade R (2007) Beta and alpha electroencephalographic activity changes after acute exercise. Arq Neuropsiquiatr 65:637–641

38. Pisinger C, Jorgensen T (2007) Waist circumference and weight following smoking cessation in a general population: the Inter99 study. Prev Med (Baltim) 44:290–5

39. Filozof C, Fernández Pinilla MC, Fernández-Cruz A (2004) Smoking cessation and weight gain. Obes Rev 5:95–103

40. Meyers a W, Klesges RC, Winders SE, Ward KD, Peterson B a, Eck LH (1997) Are weight concerns predictive of smoking cessation? A prospective analysis. J Consult Clin Psychol 65:448–52

41. Parsons AC, Shraim M, Inglis J, Aveyard P, Hajek P (2009) Interventions for preventing weight gain after smoking cessation. Cochrane Database Syst Rev CD006219

42. Marcus BH, Albrecht AE, Niaura RS, Abrams DB, Thompson PD (1991) Usefulness of physical exercise for maintaining smoking cessation in women. Am J Cardiol 68:406–407

43. Oh H, Taylor AH (2014) Self-regulating smoking and snacking through physical activity. Health Psychol 33:349–59

44. Blundell JE, King NA (2000) Exercise, appetite control, and energy balance. Nutrition 16:519–522

45. Taylor AH (2010) Physical activity and depression in obesity. In: Bouchard C, Katmarzyk PT (eds) Adv. Phys. Act. Obes. Human Kinetics, Champaign, IL, pp 295–298

46. Ussher M, Lewis S, Aveyard P, et al (2015) Physical activity for smoking cessation in pregnancy: randomised controlled trial. BMJ 350:h2145

47. Taylor AH, Everson-Hock ES, Ussher M (2010) Integrating the promotion of physical activity within a smoking cessation programme: findings from collaborative action research in UK Stop Smoking Services. BMC Heal Serv Res 10:317

48. Everson-Hock ES, Taylor AH, Ussher M, Faulkner G (2010) A Qualitative Perspective on Multiple Health Behaviour Change: Views of Smoking Cessation Advisors Who Promote Physical Activity. J Smok Cessat 5:7–14

49. Everson ES, Taylor AH, Ussher M (2010) Determinants of physical activity promotion by smoking cessation advisors as an aid for quitting: Support for the Transtheoretical Model. Patient Educ Couns 78:53–56

50. Everson-Hock ES, Taylor AH, Ussher M (2010) Readiness to use physical activity as a smoking cessation aid: a multiple behaviour change application of the Transtheoretical Model among quitters attending Stop Smoking Clinics. Patient Educ Couns 79:156–159

51. Haasova M, Warren FC, Ussher M, Janse Van Rensburg K, Faulkner G, Cropley M, Byron-Daniel J, Everson-Hock ES, Oh H, Taylor AH (2014) The acute effects of physical activity on cigarette cravings: exploration of potential moderators, mediators and physical activity attributes using individual participant data (IPD) meta-analyses. Psychopharmacology (Berl) 231:1267–75

52. Thompson T, Greaves C, Ayres R, et al (2015) Lessons learned from recruiting socioeconomically disadvantaged smokers into a pilot randomized controlled trial to explore the role of Exercise Assisted Reduction then Stop (EARS) smoking. Trials 16:1

53. Thompson TP, Greaves CJ, Ayres R, et al Factors associated with study attrition in a pilot randomised controlled trial to explore the role of exercise assisted reduction to stop (EARS) smoking in disadvantaged groups. Under Review. Trials

54. Thompson TP (2015) The design and multi-method evaluation of a pilot pragmatic randomized controlled trial of an exercise assisted reduction of smoking intervention among socioeconomically disadvantaged smokers. PhD Thesis, University of Exeter

55. Tritter A, Fitzgeorge L, Prapavessis H (2015) The effect of acute exercise on cigarette cravings while using a nicotine lozenge. Psychopharmacology (Berl) 232:2531–9

56. Asfar T, Ebbert JO, Klesges RC, Klosky JL (2012) Use of smoking reduction strategies among U.S. tobacco quitlines. Addict Behav 37:583–586

57. Farley AC, Hajek P, Lycett D, Aveyard P (2012) Interventions for preventing weight gain after smoking cessation. Cochrane Database Syst Rev 1:CD006219

58. Kaczynski AT, Manske SR, Mannell RC, Grewal K (2008) Smoking and physical activity: a systematic review. Am J Heal Behav 32:93–110

59. Van der Meer RM, Willemsen MC, Smit F, Cuijpers P (2013) Smoking cessation interventions for smokers with current or past depression. Cochrane Database Syst Rev 8:CD006102

60. DeRuiter, W. and G. Faulkner, Tobacco harm reduction strategies: the case for physical activity. Nicotine Tob Res, 2006. 8(2): p. 157-68.

61. Shahab L, Goniewicz M L, Blount BC, McNeill A, Alwis KU, Feng J, Wang L, West R (2017) Nicotine, carcinogen, and toxin exposure in long-term e-cigarette and nicotine replacement therapy users: A cross-sectional study. Ann intern med, 21; 166 (6): 390-400.

62. Bryman J (2001) Social Research Methods. Oxford University Press, Oxford

63. Thompson et al. (under review; Taylor et al. (HTA final report from EARS).

64. Wormald H, Waters H, Sleap M, Ingle L (2006) Participants' perceptions of a lifestyle approach to promoting physical activity: targeting deprived communities in Kingston-upon-Hull. BMC Public Health 6:202

65. Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P (1998) Qualitative research methods in health technology assessment: a review of the literature. Health Technol Assess (Rockv) 2:1–276

66. Curtis L (2014) Unit Costs of Health and Social Care 2014. PSSRU, University of Kent

67. Coleman T, Agboola S, Leonardi-Bee J, Taylor M, McEwen A, McNeill A (2010) Relapse prevention in UK Stop Smoking Services: current practice, systematic reviews of effectiveness and cost effectiveness analysis. Heal Technol Assess 14:1–152, iii–iv

68. Vogl M, Wenig CM, Leidl R, Pokhrel S (2012) Smoking and health-related quality of life in English general population: implications for economic evaluations. BMC Public Health 12:203

69. Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, Bonsel G, Badia X. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of Life Research.

70. Ware JE, Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34:220–233.

71. EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208

72. Devlin, N., Shah, K., Feng, Y., Mulhern, B. and Van Hout, B. Valuing Health-Related Quality of Life: An EQ-5D-5L Value Set for England. Office for Health Economics (Discussion Paper). January, 2016.

73. Brazier J, Ratcliffe J, Salomon J, Tsuchiya A. Measuring and Valuing Health Benefits for Economic Evaluation. Oxford: Oxford University Press; 2007.

74. Heatherton TF, Kozlowski LT, Frecker RC, Rickert W, Robinson J. Measuring the heaviness of smoking: using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. British Journal of Addiction. Volume 84, Number 7 (July 1989) 791-799.

75. Aveyard P, Wang D, Connock M, Fry-Smith A, Barton P, Moore D. Assessing the outcomes of prolonged cessation-induction and aid-to-cessation trials: Floating prolonged abstinence. Nicotine & Tobacco Research, Volume 11, Number 5 (May 2009) 475–480.

76. Bryman J (2001) Social Research Methods. Oxford University Press, Oxford

77. Smith JA, Jarman M, Osborn M (1999) Doing Interpretive Phenomemological Analysis. Qual. Heal.Psychol. Theor. Methods

78. Wormald H, Waters H, Sleap M, Ingle L (2006) Participants' perceptions of a lifestyle approach to promoting physical activity: targeting deprived communities in Kingston-upon-Hull. BMC Public Health 6:202

79. Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P (1998) Qualitative research methods in health technology assessment: a review of the literature. Health Technol Assess (Rockv) 2:1–276

80. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.

81. Van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health. 2012;15(5):708-15.

27 APPENDIX 1 - AMENDMENT HISTORY

Amendment Number	Protocol Version Number	Date Issued	Author(s) of Changes	Details of Changes Made
1	2		Helen Hancocks	Section 7.3 – Addition of Docmail®. Section 7.5 – SF-12 description moved from Section 19.1. Section 8.6.3 – Clarification that reminder phone calls to non-responders may be performed by local study staff such as administrative staff at the GP practice and are subject to local permissions. Section 18.1.5 – Clarification that all process evaluation interviews will be audio recorded, but not all will be fully transcribed, some will only be summarised as notes. Section 19.2 – Removed duplication of the whole section.

28 APPENDIX 2 - CODE FOR SAMPLE SIZE CALCULATIONS

Stata:

```
set more off
power twoproportions 0.05 0.11, test(fisher) n(884 (2) 916) graph(yline(0.9) plotopts(mlabel(N)
mlabsize(vsmall) mlabpos(11))) table(, formats(alpha_a "%7.3f" power "%7.3f"))
```

R:

```
library(Exact)
pow <- NULL
n <- NULL
#pow <- matrix(c(n1), ncol=1, nrow=2)
for (i in 1:20) {
  n[i] = 440 + i
    pow[i] <- (power.exact.test(0.05,0.11,n[i],n[i],alpha=0.05, alternative="two.sided",
method="fisher")$power)
    #print("Group size = ",[i],pow$power)
}
power.table <- cbind(n,pow)
```