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The Preloading trial

An open label pragmatic randomised controlled trial of nicotine preloading for smoking cessation

Version 6.0

30/07/2013

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Chief Investigator:	*Professor Paul Aveyard*
Study Co-ordination Centre:	*Primary Care Clinical Trials Unit (PC-CTU)*

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This protocol describes the Preloading Trial and provides information about procedures for entering participants: it should not be used as a guide for the treatment of other participants. Every care has been taken in the drafting of this protocol, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres entering participants for the first time are advised to contact the trials centre to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the Study Co-ordinator.

This study will adhere to Good Clinical Practice and will be conducted in compliance with this protocol, the Data Protection Act, and other regulatory requirements, as appropriate.

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1 TRIAL SUMMARY

1.1 Title

An open label pragmatic randomised controlled trial of nicotine preloading for smoking cessation

1.2 Aims

To examine the relative efficacy, safety and cost effectiveness of standard NHS stop-smoking treatment versus standard treatment plus nicotine patch worn for 4 weeks prior to quitting.

1.3 Outcome Measures

-Six month prolonged abstinence, measured according to the Russell standard criteria, i.e. a grace period of 2 weeks, followed by smoking fewer than 5 cigarettes thereafter and biochemically confirmed by an exhaled CO of <10ppm (primary outcome)
-Efficacy- abstinence measured according to Russell standard at four weeks and 12 months post-quit, and 7-day point prevalence, biochemically confirmed abstinence at 4 weeks, 6 and 12 months post-quit.
-Side-effects of NRT patch use and symptoms of nicotine overdose (such as nausea, watering mouth) at each contact.
-Costs of behavioural support and NRT, in order to calculate cost/lifetime quitter, the cost/life year gained and the cost/quality adjusted life year, and health service use.

1.4 Population

Smokers in England, seeking cessation support.

1.5 Number of Sites

The various sites are within the West Midlands; Bristol, London and Nottingham (Appendix C). New sites may be added as necessary to meet recruitment targets.

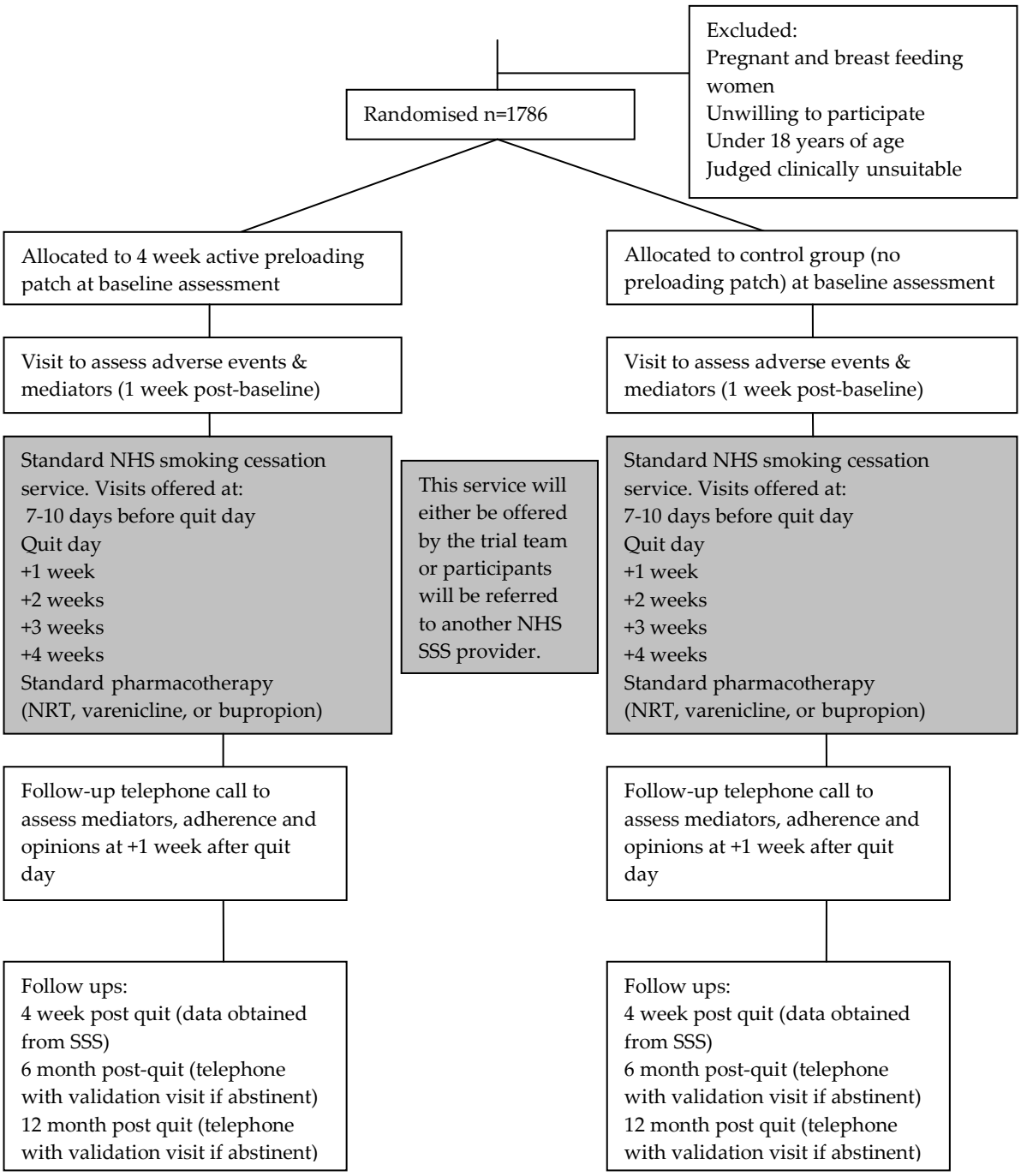
1.6 Eligibility

Smokers aged ≥18 years of age (assessed on telephone screening), suitable for preloading (assessed on telephone screening and in clinic), seeking support to stop smoking, and willing to quit in 4 weeks.

1.7 Duration

Each participant shall be enrolled for roughly 4 weeks pre-quit day and followed up for 12 months post-quit.

1.8 Trial flow diagram



2 INTRODUCTION

2.1 Background

People who try to stop smoking typically experience urges to smoke, often described as cravings, frequently in response to environmental cues associated with smoking (such as drinking alcohol). These urges decrease in intensity and frequency with time. The key to stopping smoking is to resist these urges. Effective medication for smoking cessation reduces the intensity of the urges[1, 2], and this is the likely mechanism of action.

There are three licensed medications for smoking cessation: bupropion, varenicline, and nicotine replacement therapy (NRT). Varenicline is a nicotinic partial agonist and it is therefore surprising to find that it is more effective than a full agonist, nicotine[3].An investigation considered the possible mechanisms of action and compared varenicline, bupropion, and placebo[4]. It found that varenicline reduced urges to smoke to a lower level than did bupropion. Furthermore, varenicline led to lower satisfaction from a lapse (smoking episode) after quit day than did bupropion. However, many other mood related symptoms of withdrawal were of similar intensity. This suggests that a key mechanism of action of the smoking cessation pharmacotherapies, that relates directly to efficacy in promoting cessation, is controlling urges and reducing satisfaction from smoking. Unlike NRT, varenicline is used for at least a week and up to two weeks prior to quit day, which might explain superior efficacy. Using NRT while smoking reduces satisfaction from smoking[5] so it seems logical to examine whether NRT used prior to quitting could make smoking cessation more successful. This is nicotine preloading.

It is important to note that the mechanism proposed above is widely assumed to underlie the apparent effectiveness of preloading. It is also worth noting that, if true, it should work independently of whether or not a person uses pharmacotherapy after cessation, or the type of pharmacotherapy that is used. The proposed mechanism is essentially that nicotine preloading reduces the reward from smoking, and this begins to undermine the learned association between smoking and reward.

2.2 Evidence from systematic reviews and meta-analyses

There are two previously published systematic reviews of nicotine preloading [6, 7]. These reviews both reported very positive results for preloading, with Shiffman & Ferguson giving an odds ratio (OR) of 1.96, 95% confidence interval (CI): 1.31–2.93 for six weeks abstinence, and an OR of 2.17, 95% CI: 1.46–3.22 for six months. The Cochrane review gave an RR of 1.79 (95% CI=1.17, 2.72) for long-term abstinence (6 or 12 month).

In preparing the application for the reported trial, we undertook an updated meta-analysis[8]. This meta-analysis also investigated three hypotheses to examine the possible mechanisms of action and help explain the variation in results observed in

the existing clinical trials. We have reproduced the main findings of this review below. Compared with the previous published reviews, we included four more studies and the evidence was based on a meta-analysis of 2813 participants.

First, our review showed much less evidence of efficacy than the earlier reviews. There was a weak, positive, but non-significant effect of preloading versus placebo/no treatment on short-term abstinence (RR= 1.05, 95% CI= 0.92, 1.19), p=0.49, with marked heterogeneity (I^2 of 69%, p=0.002). The effect on long-term abstinence gave a slightly larger but not significant RR of 1.16 (95% CI=0.97, 1.38), with less heterogeneity, I^2=36%, p=0.14. Indirect comparisons, however, suggested that longer acting NRT (e.g. patch) might be more effective than shorter-acting types (e.g. gum/ lozenge); RR for short term cessation using patch was 1.17 (95% CI= 1.00, 1.37) and, for gum/lozenge was 0.82 (95% CI= 0.66, 1.02), p= 0.009 for the difference in RRs. For longer term cessation the RR were (for patch) 1.26 (95% CI= 1.03, 1.55) and, for short-acting NRTs RR of 0.87 (95% CI= 0.60, 1.26), although the difference between the sub-groups was not statistically significant (p=0.09). There is good evidence that smoking on a patch leads to higher blood nicotine concentration than when smoking alone. However, smoking while using short-acting NRT leads to concentrations similar to that while smoking alone,[9] and this difference in response to smoking while using these types of NRT might explain the apparent difference in efficacy between patch and other NRT.

Second, we examined whether there was evidence to suggest that preloading works because it reduces positive or negative reinforcement from smoking and there was modest support for this. One study[5] reported reduced reward and one trial[10] reported no effect on positive reinforcement. Four studies[5, 10-12] reported data relevant to negative reinforcement of smoking (feeling the need to smoke to stave off withdrawal) and none found evidence of this effect. However, we would expect that reduced reinforcement of cigarettes or reduced need to smoke should result in reduced consumption and this was observed. In five studies[5, 10, 11, 13, 14] where participants were asked to smoke as they wanted to do, there was a variable reduction in cigarettes per day, with a smaller and variable reduction in biological markers of smoke intake. One study, Schuurmans[12], asked participants not to change their smoking and little reduction in consumption was noted. Studies in which participants were asked to reduce consumption showed the largest decline in consumption[15, 16]. These studies used short-acting NRT to support reduction, which showed no evidence of efficacy over standard NRT use. The final part of this potential pathway is that reduced reinforcement from smoking leads to reduced withdrawal after cessation, but six studies showed no evidence of this[5, 10-13, 16].

Our second meditational hypothesis was that nicotine preloading worked because it enhanced adherence to post-cessation NRT. In all trials[5, 10-16], nicotine preloading was followed by nicotine post-cessation pharmacotherapy. There is good evidence

that adherence to NRT (patch or short-acting) enhances cessation [17, 18]. Four studies reported data and none of these showed enhanced adherence post-cessation[12, 14-16]. As two of these studies were 'positive' studies[12, 14], this is good evidence that NRT preloading does not enhance cessation through enhanced post-quit day adherence to NRT.

Our third hypothesis was that preloading enhanced confidence in quitting, which has been shown to be moderately associated with enhanced cessation success.[19] Two studies[15, 16] reported contradictory data, but this indicates no good evidence to support this hypothesis.

We concluded that there was insufficient evidence to recommend preloading as a strategy for use routinely and that further trials were needed to confirm effectiveness. Second, the best supported hypothesis was that preloading may work by altering the need or desire to smoke. The trials were heterogeneous in ways that defied easy explanation. Bullen, for example, used mainly nicotine patches like the other 'positive' studies and reported reasonable adherence with preloading medication, but no good evidence of efficacy in a large study[13]. This raises the possibility that there is true heterogeneity in response to preloading with nicotine patches. Some people may benefit and others not benefit from preloading.

Investigating mediation is important. First, it could explain variation in response to preloading across studies. It would have been helpful for all studies to have recorded mediators and reported these fully. Variation in response to the mediator is likely to give a much clearer signal about the efficacy of a particular strategy for preloading than is longer-term abstinence. We do not want to add another inexplicable result to the meta-analysis showing heterogeneity. Second, it has important practical implications for treatment. Instituting preloading in the NHS Stop Smoking Service would cost about £50 million. If preloading was effective for only half of users, it would be useful to know which half. If we could monitor response to treatment i.e. monitor a mediator, then we might be able to stop preloading in patients who are not responding. This could save tens of millions of pounds. Alternatively, we could use the patient's response measured by the mediator to adjust treatment (such as dose, duration, or form of medication) to enhance efficacy. Hypertension trials almost always monitor blood pressure (mediator) in addition to primary outcomes (morbidity and mortality).

2.3 Rationale for Current Trial

A further trial of nicotine preloading is required to improve the precision of the estimate of effect of preloading, to try and establish the cause or causes of the heterogeneity in the current trials, and to enhance understanding of the mechanisms and moderators of action. By improving understanding of these mechanisms clinicians may have a basis for deciding which patients would benefit from preloading, and therefore be able to offer targeted cost effective treatment.

2.3.1 Rational for measuring weight change

Eighty percent of smokers gain weight when they quit [20, 21], which offsets some of the benefits of quitting.[22-24] Meta-analysis of data from the control arms of smoking cessation trials shows that people who achieve continuous abstinence gain a mean of 4kg at six months and 5kg at 12 months.[25] Some observational data shows those who relapse to smoking revert to their smoking weight.[20, 26] However, more evidence is required to confirm this. This is important because smokers characteristically make many attempts to stop smoking. If each attempt is associated with an increment in weight gain, then attempts to stop smoking could lead to a very large eventual weight gain. This study is not ideal for assessing weight gain and subsequent loss on relapse, because we have no clinical contacts after quit day until the long-term follow-ups at six and 12 months. However, by assessing weight in all smokers at longer follow-ups, we will be able to see whether there has been weight gain beyond that expected from population norms.[27]

The second issue is that we have only scanty and somewhat contradictory data on predictors of weight gain [28]. Although the mean weight gain is relatively modest at 5kg at one year, the variability is large with a standard deviation of 4kg [25]. This shows that some people gain much more than the mean - about 15% gain more than 10kg in a year. It would be helpful to identify these people before they quit smoking and ensure that they were offered programmes known to prevent some weight gain.[29] It seems likely that past weight gain on quitting may be an important risk factor for weight gain in a current quit attempt. One study suggests this but the data are scant.[30] Other baseline characteristics that have been identified as possible predictors in several prospective cohorts include daily cigarette consumption, tobacco addiction severity, age, gender, socioeconomic status, ethnicity, baseline BMI, heaviest weight to date, alcohol consumption.[28, 31-33] We will therefore use this large smoking cessation study to create a model that might be used in the future to predict who would gain excessive weight, and therefore who might be offered special interventions to prevent this. To do so, we will use only those variables that either are routinely or could routinely be measured in a smoking cessation clinic.

2.3.2 Rationale for the collection of genetic data

Smoking behaviours, including heaviness of smoking and smoking cessation, are known to be under a degree of genetic influence,[34] and elucidating the genetic predictors of smoking behaviours may help to develop new pharmacotherapies for smoking cessation, or identify sub-groups for whom more intensive support may be necessary. For example, we recently reported evidence for a moderating effect of catechol-*O*-methyltransferase (*COMT*) rs4680 genotype on the relative efficacy of nicotine replacement therapy (NRT) transdermal patch compared to placebo.[35] NRT produced relatively greater benefit compared to placebo in producing abstinence in individuals with the *COMT* AA (Met/Met) genotype, compared to those with either the AG (Met/Val) or GG (Val/Val) genotype. We subsequently replicated this

association of the A (Met) allele with improved response to NRT in an open-label trial of the NRT transdermal patch.[36] However, future studies will most likely require the use of genome wide association methods to identify novel genes associated with smoking cessation, for which large samples are required. Therefore, the collection of additional genetic data within clinical trials of smoking cessation is necessary to augment existing samples, such as the Patch II and Patch in Practice trial samples which some of the investigators hold.[37]

2.3.1 Rationale for a control intervention

The control arm of this trial will not receive a placebo treatment, which could lead to bias. This is because participants in the control arm may feel that they are not receiving an intervention and therefore be less likely to continue in the trial after allocation to trial arm. This could lead to differential drop-out in the two study groups. Additionally a lack of treatment in the control arm could mean that participants receive less contact or interaction with the researcher, leading to variability in efficacy in itself. In order to counteract this potential bias, and to engage participants in the control arm, we propose a minimal intervention in the control arm, comparable to the intensity of the preloading treatment, but unlikely to influence efficacy (Section 8.1).

3 TRIAL OBJECTIVES

1. To examine the relative efficacy of nicotine patch worn for 4 weeks prior to quitting plus standard NHS care post-quit versus standard care only in smokers undergoing NHS treatment for tobacco dependence.
2. To examine the safety of the nicotine pre-treatment.
3. To examine the incremental cost-effectiveness of nicotine pre-treatment.
4. To examine possible mediating pathways between nicotine pre-treatment and outcomes.
5. To measure weight change over the course of the study, predictors of this weight change, and the impact that smoking relapse has on this.
6. To examine moderators of the effects of preloading, including demographic characteristics, previous use of pharmacotherapy to quit, smoking history and baseline levels of dependence.
7. To investigate opinions of the preloading intervention.
8. To assess adherence to preloading treatment and subsequent standard smoking cessation pharmacotherapy.

4 TRIAL DESIGN

4.1 Plan of Investigation

Open label pragmatic randomised controlled trial to compare 893 motivated to quit smokers using a determined dose of nicotine patch for 4 weeks prior to

quitting, with 893 of the same type of participants randomised to a control group of standard NHS treatment, with no placebo.

4.2 Trial Outcome Measures

1. Six month prolonged abstinence, measured by the Russell standard criteria i.e. a grace period of 2 weeks, followed by smoking fewer than 5 cigarettes thereafter and biochemically confirmed by an exhaled CO of <10ppm (primary outcome).
2. Russell standard four week and 12 month prolonged abstinence and 7-day point prevalence biochemically confirmed abstinence at 4 weeks, 6 and 12 months (secondary outcomes).
3. Side-effects of NRT patch use and symptoms of nicotine overdose (such as nausea, excessive salivation) at each contact.
4. Costs of behavioural support and NRT, in order to calculate cost/lifetime quitter, the cost/life year gained and the cost/quality adjusted life year, and health service use.
5. Markers of potential mediators of the preloading effect, such as changes in expired air CO between baseline and quit date, aversion/nausea, dependence, ratings of smoking reward, urges to smoke, stereotypy, confidence in quitting, motivation to quit.
6. Change in participant weight from baseline to follow-ups.
7. Markers of potential predictors of the change in weight from baseline to follow-ups.
8. Markers of potential moderators of the preloading effect, including demographic characteristics, previous use of pharmacotherapy to quit, smoking history and baseline levels of dependence.
9. Participant ratings of helpfulness, whether they would recommend preloading, and other views about the intervention.
10. Adherence to preloading in pre-quit period, and adherence to additional standard smoking cessation medication.

4.3 Study Timetable

Trial Task	**Month:**	-3-0	0-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-31	32-36	37-42
Ethics, MHRA, practice recruitment													
Patient recruitment, data collection													
6 and 12 month follow ups													
Futility analysis													
Data cleaning, database lock (month 25), analysis, write up													

5 PARTICIPANT ENTRY

5.1 Sample Size

893 participants in each of the two treatment groups; 1786 in total.

5.2 Recruitment

We propose recruiting people in the following ways:

Recruitment centres in Birmingham, Bristol and Nottingham will recruit through GP practices. GP surgeries will be asked to write to patients who are listed as smokers on their clinical database, asking them to call the research team if they are interested in participating in the trial. The letter will encourage the person to stop smoking and to take the opportunity to enrol in the trial as a means of doing so. The content of the letter is therefore similar to a conversation between a GP and a patient. In some practices, as well as or instead of sending letters (depending on the circumstances within the practice), we will ask practices to send out text messages to smokers advertising the trial using their text messaging system, and will ask them to give out fliers advertising the study with patient's repeat prescriptions. Again, interested patients will be provided with the contact details of the trial team. Additionally, we will give GPs referral cards detailing the telephone recruitment number to give to their patients who smoke, display advertising posters in GP practices, and provide GPs with mouse mats reminding them about the trial and to refer participants who are smokers. Screening will not take place at this stage, other than identifying the patient as an adult smoker. Screening will take place when a potential participant contacts the trial team to express interest in taking part.

To supplement recruitment where necessary these three centres will also ask NHS health services, such as GP practices and NHS Stop Smoking Services, and potentially community venues if they have rooms for the research team to use to conduct clinics to recruit participants from a wider area, i.e. the wider community, as well as existing patients. This will offer centralised clinic locations, and so will allow for a wider range of advertising possibilities. We will advertise for smokers to join the trial clinics held in these central clinic locations using methods as follows:

- Newspaper/magazine/internet advertisements
- Posters and fliers advertising the study distributed and displayed within the community
- The study will be advertised in or alongside payslips distributed at the recruitment centres
- Stop smoking services will be asked to write to people who have used their services in the past and are believed to still be smokers, inviting them to take part in the trial.
- Researchers will see if it is appropriate for them, and seek agreement from individual stop smoking services, to inform smokers booked to attend the service about the possibility of taking part in the trial before their first appointment. Researchers will then enrol anyone who wishes to take part

and refer them back into the stop smoking service after their trial treatment (i.e. preloading or coping treatment).

- Recruitment centres are running a number of studies in their University departments. In cases where participants would be appropriate to take part in the Preloading trial (i.e. adult smokers not already quitting), participants will be provided with a referral card or leaflet advertising the trial.

At the additional recruitment centre (London) participants will be recruited at an existing NHS smoking cessation clinic which accepts self-, primary care- and secondary care- referrals. This final centre will offer patients, who present to this clinic for treatment, the chance to participate in the clinical trial, and will act as a site. The NHS Stop Smoking Service is one of the few NHS services that advertise for patients. At this site, we therefore will also use advertising as necessary to supplement recruitment into the trial, as would usually take place.

5.3 Pre-Randomisation Evaluations

Potential participants will telephone the trial office for further details of the trial. The office personnel will give information about the study, and if the potential participant wants to be screened for eligibility, will then use the online database to assign them an ID number and perform preliminary eligibility screening (see inclusion/exclusion criteria below). ID numbers will be allocated at this stage regardless of whether the participant goes on to be randomised to ensure that we keep track of all interest expressed in the trial, and so that all paperwork is traceable. However, only if the screening is successful will we ask potential participants to provide any personal contact details. In this case we will send the potential participant a patient information sheet and an appointment at a clinic to attend for fuller discussion with the researcher (See Section 7.1 for researcher characteristics), signing the consent form, further screening, and trial entry procedures. In three of the four centres, we will use the participant's own GP surgery or a local Stop Smoking Service clinic location as the venue for the initial meeting and this may or may not be the venue where the participant receives NHS smoking cessation support, depending on the surgery/service. In the fourth centre, the initial meeting will take place in the London based smoking cessation clinic.

To be recruited on the trial, participants need to fulfil the inclusion criteria stated below.

5.4 Inclusion Criteria

- Smokers (defined as regular smokers of cigarettes, cigars, and tobacco cigarettes combined with marijuana) aged ≥18 years of age (assessed on telephone screening and in clinic)

- Smokers who, in the judgement (see below for how judgement shall be made) of the trial researcher, would be suitable for preloading (assessed on telephone screening and in clinic).
- Seeking NHS support to stop smoking and willing to quit in 4 weeks (assessed on telephone screening and in clinic)
- Able to understand and consent to, and willing to comply with, study procedures (assessed on telephone screening and in clinic).

5.5 Exclusion Criteria

- Pregnant or breastfeeding (assessed on telephone screening and in clinic)
- Extensive dermatitis/other skin disorder that precludes patch use (assessed on telephone and clinic screening)
- Acute coronary syndrome or stroke within the past three weeks (assessed on telephone screening and in clinic)
- Active phaeocromocytoma and uncontrolled hyperthyroidism (assessed on telephone screening and in clinic)

Judgement of suitability will aim to include more addicted smokers and exclude smokers with such low levels of addiction that the preloading patch may cause unacceptable toxicity. It will be based upon the following criteria:

- Time to first cigarette in the morning with earlier use reflecting higher addiction;
- Number of cigarettes smoked per day with a greater number reflecting higher addiction;
- Higher exhaled CO, which reflects higher addiction;
- Failure of previous quit attempts despite use of appropriate pharmacotherapy.

5.6 Withdrawal Criteria

Trial withdrawal: Should participants wish to withdraw from the trial, they will be given every opportunity to do so. It is standard practice in smoking cessation trials to regard those who fail to attend for support and treatment as having relapsed, which is based on some evidence.[38] Therefore, failure to attend will not count as withdrawal from the trial and the only withdrawals will be those where a patient asks to be withdrawn. Such patients will not be replaced and, unless s/he refuses permission, data available up to that point will be used. Such withdrawals are expected in fewer than 5% of participants.

Treatment withdrawal: We will exclude from the trial all those who have had severe adverse reactions previously. Given the established safety profile of NRT and the evidence from studies of participants using NRT while smoking[9], we do not expect any serious adverse events due to the medication. Nevertheless, there will be a detailed work instruction for the trial that will detail the assessment of adverse events, and the procedure for defining and managing

serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSARs). In the event of a SUSAR, or SAR judged either possibly, probably, or definitely related to NRT, the prescription for NRT will be withdrawn and not re-instituted in that person. The person will continue in the trial and be part of both the safety and efficacy populations.

6 RANDOMISATION AND ENROLMENT PROCEDURE

6.1 Randomisation or Registration Practicalities

Participants shall be randomised to a treatment arm at their baseline visit. In three of the four research centres, this will take place at the participants' own GP surgery or at a local stop smoking service clinic location. In the fourth site, the initial meeting will always take place in the London-based smoking cessation clinic.

Participants will be randomised to the intervention or control (1:1 ratio) on the basis of a computer-generated allocation sequence via the internet, with telephone back-up, which will be provided by our ePCRN http://www.epcrn.bham.ac.uk/. This will incorporate an online case report form (CRF) that, when basic details have been completed, will accomplish randomisation. We will block randomise participants, stratified by centre- to account for the differences in recruitment and treatment delivery between the London research centre and the remaining centres. For very rare occasions when access to the network, and therefore database randomisation is not available, we will have a back-up process involving sequentially numbered, opaque sealed envelopes for randomisation. Each researcher will hold a small number of envelopes; to be used as a last resort only.

It is common for two people, often partners, to want to quit together. There is no imperative for the couple to be given the same treatment, as the absence of placebo means mixing up medication is unlikely, and non-randomly allocating a person to the same intervention as their partner may introduce clustering effects. Therefore in these cases we will ask participants to consent to separate allocations.

7 STUDY PROCEDURES

7.1 Trial treatment providers

The provision of participant treatment in the trial shall be carried out by researchers from both a clinical and non-clinical background. All shall be trained by the NHS Stop Smoking Service (SSS) and the National Centre for Smoking Cessation and Training (NCSCT) to provide stop smoking support and to advise and provide all pharmacotherapies available through the NHS

SSS. This is the maximum equivalent to what is required for NHS SSS advisors. In addition to this all researchers will be provided with trial specific and Good Clinical Practice (GCP) training. However in the case of any uncertainty (i.e. regarding suitability for inclusion) researchers will be able to contact the PI for the relevant site for clarification by telephone. If the PI for the relevant site is not contactable then they shall contact another of the trial PIs. PIs will only delegate tasks relevant to the researchers' training and experience.

7.2 Provision of standard NHS SSS support

In addition to the research visits carried out below, all participants will receive standard NHS SSS support and medication whilst enrolled in the trial. One of the centres involved in this study (Queen Mary, London) hosts an existing NHS SSS clinic operating within the East London Stop Smoking Service. All participants recruited through this site will be provided with both trial support and treatment (as outlined in Section 7.3) and standard NHS SSS support and treatment by the research team. Therefore participants will be booked in for standard support at the baseline trial visit. The remaining three centres will be recruiting through GP practices and local stop smoking services across a number of trusts. In some trusts and practices it may be most favourable (where local funds allow and a service is not already provided within the GP practice) for the research team to carry out both the trial and standard NHS SSS procedures (acting on behalf of the local NHS SSS- as above), whereas for others it may be most favourable to refer participants to their local NHS SSS for their standard treatment (where local funds do not allow and a local service convenient to the patient is provided). In which case the research contacts described below would be carried out by the research team and the standard support by the NHS SSS. In cases such as this researchers will book participants into a local NHS SSS clinic at the baseline research visit, and a link will be made with the local NHS SSS requesting the date of quit day and four-week quit data for the participants concerned. In a previous trial this has been achieved by requesting reports from the stop smoking services, however more and more services are using a centralised database, which the trial team will request access to. Consent will be requested from participants to access their stop smoking service records. Where appropriate, where the study team will only be conducting research activities and will not be providing any standard NHS support, GP practices and Stop Smoking Services may be asked to act as participant identification centres (PICs) only. In this case GPs will be asked to inform their patients who are smoking about the trial and ask if they would like to take part (as described previously), and in some cases asked to hire a room out to the study team, which will be used to carry out the research activity.

7.3 Research contacts

Visit 1 – baseline – enrolment

The purpose of this visit is to explain the trial and seek written consent for any further trial procedures. These include further screening for participant eligibility, and randomisation if the participant is eligible. The researcher will also collect basic data, take relevant samples, dispense the preloading and provide support to enhance adherence to NRT. Data to be collected by the researcher at this visit is reported in Table 1.

Table 1 : Data collection to take place at the Baseline Visit

Data to be collected
Medical problems and concomitant medication
Basic demographic information (date of birth, gender, ethnic group, educational qualification, occupational classification), information on smoking history (cigarettes per day, age at commencement, dependence, longest period of previous abstinence), and exhaled CO.
Previous use of pharmacotherapy for cessation and experiences of doing so, to assess suitability for treatment, and to examine whether it moderates the efficacy of preloading.
Baseline health care use (including primary care and secondary care visits) for economic analysis.
Participant weight using self report and weighing scales. As relapsers will not attend clinic at 6 and 12 month follow-ups the difference between self reported and measured weights will be applied as a corrective adjustment to self reported weight at follow-up in these participants.
Baseline measures to allow future assessment of change in potential mediators of the preloading effect, such as dependence, nausea from smoking, reward from smoking, urges to smoke, smoking stereotypy, confidence in quitting, motivation to quit.
Additional baseline measures to allow future assessment of predictive ability of variables on weight change from baseline to follow-up: cigarettes per day, dependence, gender, educational qualification, occupational classification, height, age, ethnicity, alcohol intake, heaviest weight to date, previous quit attempt weight gain.
Blood sample to identify genetic information (this will only take place at research centres with the resources to do so, where researchers are trained in phlebotomy, and will be optional for participants).
Salivary sample to measure cotinine concentration (the best measure of smoking intensity)

Visit 2 - one week after enrolment

The purpose of this visit is to examine adverse events, to see whether they are due to preloading, in accord with GCP, to collect a measure of exhaled carbon

monoxide (CO), to assess adherence to preloading in the preloading trial arm, to collect a salivary sample for cotinine measurement and measure other potential mediators described in Visit 1. If this visit reveals problems with adverse events or requires alteration of the dose of the preloading patch, further visits and/or telephone calls will be scheduled as seems appropriate to the researcher or PI.

In the control group, this visit has no therapeutic or safety purpose and is there solely for us to collect data. We therefore propose to compensate all participants for returning for this visit with £15 as compensation for travel expenses and the time involved.

Every effort will be made for this visit to take place exactly one week after baseline; however in cases where this is not possible visit 2 will take place between week -3 and week 0, before data is classed as lost to follow-up.

Telephone call one week after quit day

During this telephone call from the researcher to the participant, potential mediators will be measured as described in Visit 1, as well as adherence to the nicotine patches during the preloading period, and opinions of the preloading intervention.

Every effort will be made for this contact to take place exactly one week after each participant's quit day; however in cases where this is not possible this contact will take place between +5 days after quit day and week +4, before data is classed as lost to follow-up.

In some cases a participant may reach their quit date and fail at this attempt. In this case participants may reset their quit date. However as per NHS SSS guidelines this reset quit date would be classed as a new quit attempt by the service. For the purposes of this study the original quit date will also be classed as the quit date and this date will inform follow-ups.

Four week follow-up

As described above (Section 7.2), in some cases quit data from this follow-up will be collected by the research team, however in other cases this data will be collected by NHS smoking cessation services operating outside of the trial. In this case we will set up a system with the local SSS to gain access to this data. Smoking status at 4 weeks, defines abstinence as no smoking at all in the past two weeks, confirmed by CO<10ppm.

Six month telephone and clinic follow-up

We will telephone participants at six months after quit day to establish abstinence, measure relevant mediators, and take self-reported weight

measurement. Participants who declare that they are abstinent will be invited to return to clinic for exhaled CO measurement to confirm this, as is standard. A weight measurement will also be taken, using weighing scales. As this is not a therapeutic visit, participants returning for the visit will be compensated £15 in lieu of travel expenses.

Every effort will be made for this contact to take place exactly 6 months after each participant's quit day; however in cases where this is not possible this contact will take place between 2 weeks prior to 6 months post-quit and month +9, before data is classed as lost to follow-up.

12 month telephone follow-up

We will telephone participants at 12 months post-quit day to establish abstinence, health care use, measure relevant mediators and predictors, and weight measurement by self report. Those who report not smoking will be invited to clinic to measure CO, and weight, using scales. As this is not a therapeutic visit, participants returning for the visit will be compensated £15 in lieu of travel expenses.

Every effort will be made for this contact to take place exactly 12 months after each participant's quit day; however in cases where this is not possible this contact will take place between 2 weeks prior to 12 months post-quit and month +15, before data is classed as lost to follow-up.

At the time of booking baseline, 6 month and 12 month clinic visits participants will be sent an appointment letter with the date, time and location of their appointment. In addition participants will be sent a reminder text 24 hours before each clinic visit (visit 1, visit 2, 6 month, 12 month) to help to ensure that they remember the appointment and maximise follow-up rates.

8 TREATMENTS

8.1 Treatment Arms

Intervention

The active intervention is a 21mg Niquitin CQ nicotine patch. Participants will wear these for 4 weeks before their smoking quit day, from the day of their enrolment. They will be advised to wear the patch for 24 hours a day initially. However, 24 hour patches can lead to problems of night time wakefulness or vivid dreams. Participants will be warned of this and anyone who has suffered from this in the past (assessed at baseline) will use the patch for 16 hours per day initially. In addition, we will warn participants to use the patch during daytime only should they suffer from difficulty sleeping. There is no evidence that 24 hour patches are more effective than 16 hour patches for cessation[6] and no

reason to assume that the effectiveness of preloading depends upon 24 hour wear. Participants will be advised to smoke as normal and avoid reducing consumption, during pre-quit patch treatment. Allowing nicotine concentrations to fall may mean cigarettes will be more rewarding, undermining suspected mechanisms[39]. We will help participants plan to keep to their consumption, for example by asking a 20/day smoker to make sure s/he empties his or her pack by bedtime if possible. However, participants will be free to reduce and not pressured into smoke if they find this difficult.

Although we aim that participants shall preload for four weeks, in some cases we will need to book participants into convenient NHS stop smoking clinics- in order for them to also receive standard NHS smoking cessation support- and some participants defer their quit date. Consequently, participants will be booked into cessation clinics to seek to ensure a target quit date between three and five weeks after enrolment. In the event that a participant has not yet reached their quit date but wishes to delay it- in particular, this may occur in the case of personal difficulties that the smoker feels will seriously impair their chances of being successful- then the participant will be able to delay their quit date to a maximum of 8 weeks following their baseline appointment, and will receive a maximum of 8 weeks worth of nicotine patches for preloading.

The manufacturer, GSK will deliver the medication to the trial centres. This is an open label RCT where medication is dispensed in clinics operating within the NHS and therefore there are no special labelling or packaging requirements. Medication will be labelled and packaged as for normal clinical use. The medication will be stored at the centres in facilities that meet the requirements of GCP. A risk assessment will take place to check the facilities for storage of the medication, to ensure that the drug will remain stable and will be stored securely, on a centre by centre basis. If the risk assessment deems it necessary we shall keep temperature logs to monitor the environment in which the medication is kept. The researchers (trained in smoking cessation treatment and medications) will dispense the medication in accord with the protocol and will record the batch numbers on the CRF, as is common practice in the NHS. Each person will usually be dispensed 2 weeks of patches initially, which is sufficient to cover treatment to the second visit but allows extra should that visit be missed. At the second visit (1 week after baseline), we will usually dispense 3 more weeks of medication to allow up to 5 weeks of preloading. The researcher will be able to use some discretion when dispensing the number of patches needed, for example to allow for cases where participants undertake a lot of exercise and so patches are likely to fall off and need replacing more commonly. The participant will not pay a prescription charge for the medication as the medication will be donated free of charge by GSK.

If participants have patches left over when they reach their quit day and they are not using nicotine patches as part of the standard NHS post-quit treatment we will encourage them to use up their patches after quitting. The rationale behind this is that otherwise we will be asking participants to stop using their patches when they are most vulnerable (on their quit day), which could contribute to failure to quit.

Control

This trial will be open label, and the comparator to preloading will be no intervention with standard stop-smoking treatment. After the participant is randomised to no intervention, s/he will begin a 4 week period prior to their quit date where NRT will not be used, to allow comparison with the intervention arm. Participants will not be advised to change their smoking behaviour in any way. As described above (Section 7.2), the control arm will also be referred to receive standard NHS smoking cessation support at the first visit, where necessary.

Trial behavioural support

In both trial arms researchers will provide behavioural support. In the preloading arm, when preloading patches are dispensed at the baseline visit, the researcher will provide support- explaining the rationale as to why nicotine preloading might be helpful, how to use the patches, including helping participants to set reminders to use the patch, providing evidence on safety and tolerability of preloading, common side-effects and how to deal with them- as well as supply a booklet describing the rationale of preloading treatment, with the aim to enhance adherence. At the -3 visit, the researcher will enquire about preloading participants' understanding of the necessity of using preloading and ask about their concerns and address these as appropriate. In the control arm, participants will not be provided with this in-depth information about preloading, but will be provided with comparative counselling. This will involve asking participants to think about the cigarettes they smoke, what triggers these and which they find most rewarding, and will be accompanied by a comparable booklet explaining the theory behind cue associated learning.

Standard NHS SSS support

The standard NHS smoking cessation support will not be in any way altered in the intervention group by the previous preloading. This cessation support typically commences 1-2 weeks prior to a target quit date and provides behavioural support typically on quit day, and then weekly until four weeks after quit day. This support addresses issues such as planning for the quit day, the 'not a puff rule', and how to deal with difficult situations, such as others smoking around the quitter. It also provides monitoring of behaviour and validation of abstinence through carbon monoxide testing. NHS providers have

had training to provide this behavioural support, largely modelled on withdrawal orientated therapy.[40] This behavioural support for cessation will therefore begin 2-3 weeks after the commencement of preloading treatment so that target quit date is 3-4 weeks after commencement. Pharmacotherapies provided as part of this support are either NRT, varenicline or bupropion and stop smoking services involved in the trial will be informed that they should provide these to participants as is usual (further information provided in Section 8.3).

8.2 Dose Modifications for Toxicity

Nicotine replacement therapy has been shown to be safe and there are no plans to modify the dose of NRT in the intervention group. However the dose of the patch may be reduced (to 14mg) in the following circumstances:

- The participant reports previous experience of adverse reactions to a 21mg patch and is not prepared to start 21mg patches
- The participant has symptoms of nicotine overdose (These include nausea, increased salivation, and pounding heart)
- The participant wishes to reduce the dose because of presumed adverse effects attributed to the patch.

The intervention will be stopped and not reinstituted under the following circumstances:

- The participant no longer wishes to use the preloading and/or decides not to proceed to a quit attempt
- Clear symptoms or signs of nicotine overdose are observed not remedied by reduced dose of patch or reduced smoking. (These include nausea, increased salivation, pounding heart).
- The participant has some intervening health state that makes continued intervention impossible, for example admission to intensive care unit
- A contra-indication to this kind of NRT use or exclusion criterion emerges e.g. the participant discovers she is pregnant

The intervention may be temporarily halted and restarted. This may occur if a participant has an intervening health or emotional crisis, such as admission to hospital as an emergency, or a bereavement. It is likely that an intervening period of smoking off the patch is likely to remove any benefit from prior preloading. In this circumstance, the participant could choose to start the preloading again, which will be allowed once. For the purposes of counting abstinence, the quit day will be deemed to have been reached a maximum of 8 weeks after the baseline visit, even if the participant is continuing with preloading and not reached quit day at this point. If we lose contact with a participant and they do not make a quit attempt, this will not count as temporary

halting of preloading and for the purpose of counting abstinence their quit day will be deemed to have taken place 4 weeks after the baseline visit.

In cases where the participant quits before their planned quit day, this day will be classed as the day they actually quit, and the timing of follow-ups will be informed by this date, rather than the date originally planned.

8.3 Concomitant Medication

All medications will be permitted for use concurrently with preloading, except those that are proven to help smoking cessation (bupropion, nortriptyline, mecamylamine, reserpine, varenicline). These will be permitted for use in the latter part of preloading in preparation for a quit attempt, but not throughout preloading. The NHS clinic will either prescribe or arrange prescription of one of three first line smoking cessation pharmacotherapies: bupropion, varenicline, or NRT (used as a single form or combination NRT) at the dose that they see fit. Bupropion and varenicline should normally commence no sooner than two weeks and at least a week prior to the quit day initially set by the Stop Smoking Service as is standard, and standard NRT use commences on quit day. The choice of medication will be determined by the smoking cessation advisor and patient in consultation and bearing in mind NICE guidance on choice. The NHS medication can continue for as long as the cessation advisor prescribes, with no special restriction imposed by the trial protocol.

NICE guidance advises against concurrent use of NRT and varenicline. However this is due to the illogicality of the combination in normal post-cessation support, rather than evidence of safety concerns[41]. Concurrent use will have to happen in this trial if preloading is followed by varenicline post-cessation support. It is possible that NHS personnel would be more inclined to prescribe varenicline in the control arm than in the intervention arm, especially as patients may be comfortable and 'responding' to NRT. We will counter this in several ways. We will give a letter to the participant to give to the NHS Stop Smoking Service therapist to explain the trial and to encourage free use of medication including varenicline. We will of course liaise with the services to ensure they know about the trial. Second, we will monitor this issue and investigate corrective actions if we see it happening with particular NHS Stop Smoking Service therapists or services. Third, we have addressed this in the analysis plan by proposing a sensitivity analysis to adjust for post-cessation medication use.

8.4 Interaction with Other Drugs

Data on all concomitant medication will be recorded. There is no special dietary or life-style advice that is imposed by using NRT and the associated regimens for using it proposed in the protocol.

8.5 Dispensing and Accountability

See above (Section 8.1).

9 TRIAL MANAGEMENT

The day-to-day management of the study will be co-ordinated by Dr Nicola Lindson-Hawley.

9.1 Roles and Responsibilities

See *Appendix A* for the roles and responsibilities of trial staff.

9.2 Trial Steering Committee

We propose a trial steering committee with a chair of Dr Michael Ussher and committee members of Dr Helen Stokes-Lampard and Dr Lion Shahab as academic members. Dr Tess Harris will also take part as an independent primary care practitioner and academic. We will incorporate a volunteer from our smokers' panel group. The UK Centre for Tobacco Control Studies has a smokers' panel to give smokers' views on our research priorities and projects. We will also incorporate an NHS service manager, to give NHS service views.

9.3 Data Monitoring Committee

Following guidance on open label and low risk trials, we have agreed with the funder (NIHR Health Technology Assessment programme) that a Data Monitoring Committee is not necessary.

10 PHARMACOVIGILANCE

10.1 Assessment of Safety

Potential participants' safety will be ensured by screening for eligibility using a structured form completed by the researcher. This will record evidence of eligibility and exclusion criteria. The researcher will be trained to assess the presence of exclusion criteria and we will provide a more detailed description of the conditions listed to aid their identification. In addition, the researcher will make an assessment of current medical problems to assess for other complicating diseases. Any queries remaining as a result of this process will be resolved by discussion between the researcher, principal investigators and the relevant physicians providing routine medical care, usually the participant's GP. Such concerns are unusual but not rare. Typically, they arise from a participant's hazy knowledge or understanding of their past medical history and are usually readily resolved. In addition, where recruitment takes place in GPs surgeries the researcher may have access to the participant's medical record and therefore may be able resolve such issues promptly. No blood or further medical testing will be necessary to ensure safety.

NRT has been investigated in several hundred previous clinical trials and is widely prescribed worldwide and subject to safety monitoring. Thus, there is every reason to expect that treatment in this trial will be safe. Fagerstrom and Hughes' review of smoking while on NRT concluded that "very few and mild adverse reactions were reported with concurrent smoking and use of NR[T], even when nicotine concentrations were elevated 2 or 3 times with use of very high doses of nicotine from patches".p77[9] These were mostly short-term studies. A systematic review of long-term NRT and concurrent smoking found no evidence of an increased rate of death or serious adverse events.[42] As the cardiovascular response profile to high dose (63mg patches) in smokers is flat, so there is no reason to assume that preloading poses problems for typical smokers.[43]

In the trials of preloading reviewed in our meta-analysis, there were no differences in the occurrence of possible side-effects or more serious problems with preloading. Of these trials, Bullen reported that the overall occurrence of adverse events was 45% vs. 45% and of serious adverse events was 18% vs. 20% in preloading and non-preloading groups.[13] Rose 1998 reported dropouts from pre-cessation treatment were due to practical difficulties.[10] Rose 2009 recorded the incidence of typical minor adverse health conditions (e.g. headache) and found the incidence similar in the pre-quitting NRT group and the placebo group [14] Schuurmans reported the incidence of adverse reactions during preloading as 6% vs 2% (not statistically significantly different) in the placebo group- all mild skin reactions.[12] Therefore preloading is safe and well tolerated.

Participants will be warned about the side-effects of NRT and advised not to stop taking the medication without consulting with an NHS professional, preferably the trial team. To this end, all participants will be given the trial team's contact details, which will allow participants to receive advice on medication or to report perceived serious adverse effects and receive advice on medication as required. Participants will record the occurrence of symptoms of nicotine overdose by completing a checklist at the one week post-baseline clinic visit. These will be given to the researcher, and they will also enquire about any other adverse events, so as to determine the severity of any adverse event and ensure that appropriate advice is given for its management (such as rotating the patch site or use of emollients for skin reactions). Minor adverse reactions will be monitored and managed in this way. For each adverse event that we anticipate encountering, the researcher will have a definition of clinical severity. For example, a mild skin site reaction to the patch will be defined as burning sensation that does not interfere with normal activities, redness or swelling at the site of application, or mild blistering. Any reaction beyond that will be classified as potentially moderate or severe and will be reported to and discussed with the

PI (or clinician delegated by the CI). A decision on stopping therapy will then be made with the participant, attending clinician, PI (or clinician delegated by the CI), and other relevant parties as appropriate. In response to the nicotine overdose schedule the researcher will make an assessment of whether the NRT dose is too high or not, and then if relevant take action, such as continue with prescribed dose, or direct the participant to use a lower dose, or reduce cigarette consumption, and these actions will be recorded.

Nicotine has a short half life (2 hours), meaning that the blood concentration will not increase during the course of treatment so that new side-effects are not expected after the first few weeks. In addition, reactions to it relate to local use, such as skin discomfort from patches and people become accustomed to the side-effects after a short time of using the preparation. At the clinic visit one week after baseline, the participant will be advised to phone the contact number provided to report side-effects that occur after this. The advice given will depend upon the severity of the reported reaction and those with moderate reactions will be invited to an ad hoc consultation.

The SmPCs for the Niquitin CQ patch contain no warnings about serious adverse reactions except rare allergic reactions, such as angioedema, and cardiac arrhythmias, occurring in less than 1/1000 users. Thus we expect no or very few SUSARs **(**suspected unexpected serious adverse reactions**)** in this trial. The long history of use in and outside of trials for NRT means that SUSARs are unlikely. Participants will be given instructions for the reporting of serious adverse events. Through direct contact from the participant or contact from their attending physician, we expect to become aware of serious adverse events. Reporting procedures and definitions are as follows.

10.2 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject, and which does not necessarily have a causal relationship with any treatment administered. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with use of an investigational medicinal product (IMP) or in the same time period in the control group, whether or not considered related to the IMP. To be counted as an AE, an event must occur during the period from baseline to 1 week after quit day. Events that occur outside of the treatment period will be noted in a significant events log in the CRF, but will not be noted as an adverse event, as they will not be related to the treatment, and so would cloud the analysis if noted as such.

Adverse Reaction (AR): all untoward and unintended responses to an IMP, related to any dose administered. All AEs judged by the reporting investigator

or sponsor as having a reasonable causal relationship to an IMP qualify as adverse reactions. The expression 'reasonable causal relationship' means to convey in general that there is evidence or argument to suggest a causal relationship.

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (i.e. the summary of product characteristics (SmPC)). When the outcome of the adverse reaction is not consistent with the applicable product information, this adverse reaction should be considered as unexpected. Side effects documented in the SmPC which occur in a more severe form than anticipated are also considered to be unexpected.

Serious Adverse Event (SAE) or **Serious Adverse Reaction (SAR)**: any untoward medical occurrence or adverse reaction that:
-Results in death
-Is life-threatening – an event in which the subject was at risk of death at the time of event, not an event that hypothetically might have caused death if it were more severe
-Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
-Results in persistent or significant disability or incapacity
-Is a congenital anomaly or birth defect

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

Medical judgement will be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or require intervention to prevent one of the other outcomes listed above, will also be considered serious. For the purpose of this trial, SAEs will be those that occur after trial enrolment until one week after quit day. If the events described above that do not occur during this period, they will not be deemed as SAEs. This is for the same reason as described in accordance with adverse events. Planned hospital admissions that occur during this period will also not be recorded as SAEs providing that the likely occurrence of these was recorded at the baseline assessment.

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious.

10.3 Causality

The assignment of the causality will be made by the investigator responsible for the care of the participant using the definitions in Table 2. If any doubt about the causality exists, the local investigator shall inform the study co-ordination centre, who will notify the chief investigator. The pharmaceutical company and/or other clinicians may be asked to advise in some cases. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

10.4 Reporting Procedures

All AEs occurring from enrolment to one week post-quit shall be reported. Depending on the nature of the event, the reporting procedures below will be followed. Any questions concerning AE reporting should be directed to the Chief Investigator, in the first instance. A flowchart is provided (*Appendix B*) to aid in the reporting procedures.

10.4.1 Non-Serious AE/ARs

All such events, whether expected or not, will be recorded in the case report form (CRF) and the electronic version of the CRF updated.

10.4.2 SAEs and SARs

All SAEs occurring during the study from enrolment to one week post-quit, either observed by the recruiting site PI or reported by the participant, whether or not attributed to study medication, will be recorded on the CRF and forwarded by the site to PC-CTU, using the "PC-CTU SAE Report Form", following assessment for seriousness and relatedness by the site clinician. This form will be completed and faxed to the PC-CTU using the number quoted on the report form. The form should also be emailed to the PC-CTU using the email address quoted on the form. As a minimum, the
following information will be recorded:

- Description
- Date of onset
- End date
- Severity
- Assessment of relatedness to study medication
- Other suspect drug or device
- Action taken.

Follow-up information should be provided as necessary.

SAEs must be reported to the PC-CTU within 24 hours of discovery or notification of the event. The PC-CTU will acknowledge receipt of the SAE Report Form using the PC-CTU 'SAE Form Receipt' document. This receipt will be emailed and faxed to the site PI. If the site PI does not receive a receipt within 24hrs of them sending the report (during office hours), they should re-send the SAE Report Form to the PC-CTU by email or fax and telephone ahead.
The documentation will be reviewed by the Quality Assurance Manager (or nominated person) and the 'SAE Checklist' will be completed and retained by the PC-CTU. Following the initial check of the report, any additional information will be requested, and the CI or their medically qualified designated representative will review and evaluate the report for seriousness, causality and expectedness, within three additional working days. In the event of a SUSAR the reporting timelines stated below should be followed. If there have been two assessments of causality made, the site PI's assessment cannot be downgraded. Where there is a discrepancy the worst case assessment is used for reporting purposes.

The PC-CTU will also ensure that SAE reports are reviewed by the Trial Steering Group at least twice during the study at teleconference meetings. TSC meetings take place at least annually and more often than that as required.

Table 2: Definitions used to establish the relationship between AEs and trial medication

Relationship	Description
Unrelated	There is no evidence of any causal relationship.
Unlikely	There is little evidence to suggest a causal relationship (eg. the event did not occur within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (eg. the participant's clinical condition, other concomitant treatments).
Possible	There is some evidence to suggest a causal relationship (eg. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (eg. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

10.4.3 SUSARs

All SUSARs will be reported by the CI to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days

10.4.3 Development Safety Update Reports

The CI will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, Host NHS Trust and Sponsor.

Contact Details for Reporting SAEs/SARs and SUSARs

Tel: 01865 617860, OR 0777 999 3126; Email: paul.aveyard@phc.ox.ac.uk;

attention of Professor Paul Aveyard

11 ASSESSMENT AND FOLLOW-UP

11.1 Assessment

Following enrolment and a baseline assessment in a GP surgery or smoking cessation clinic, participants will be followed up for roughly 13 months. One more clinic visit will take place one week following the baseline assessment. Telephone assessment will take place one week, 6 months and 12 months post quit day. Those who report cessation at 6 months and 12 months will be invited to a clinic visit to measure CO to validate smoking status and to measure weight at each of these time points. Four week smoking status will be obtained from the NHS Stop Smoking Service. As visits at baseline and the following week will be in person, questionnaires will be administered to collect some of the data outlined below. However as subsequent contacts will be over the phone data will be recorded using the CRF.

Throughout the trial abstinence shall be measured, according to the Russell Standard[38]- i.e. a grace period of 2 weeks, followed by smoking fewer than 5 cigarettes thereafter and biochemically confirmed by an exhaled CO of <10ppm- on an intention to treat basis, where participants lost to follow-up are presumed

to have relapsed. The primary outcome is six month prolonged abstinence, and secondary abstinence outcomes shall be four week and 12 month prolonged abstinence and 7-day point prevalence biochemically confirmed abstinence at 4 weeks, 6 and 12 months.

Further outcomes shall be assessed as follows:

At baseline, the researchers will collect the information stated in Section 7. Educational qualification and occupational classification will be classified in categories used in the UK Census 2011[44], ethnic group will be classified according to categories used by the NHS SSS, based on the UK Census 2001, and exhaled CO will be measured using a CO monitor, as a measure of smoke intake.

Potential mediators of the preloading effect will be assessed at baseline, one week later in the pre-quit period, one week after quit day, at 6 months and at 12 months for some measures.

Dependence will be measured at baseline using FTND[45]. The FTND will be re-administered at the week following baseline visit, and at 6 and 12 month follow-ups. However, for the purposes of the analysis, we will exclude the cigarettes per day item, which might reasonably be expected to decline in the active patch group without necessarily indicating reduced dependence.

Changes in reward from smoking- measured using the modified Cigarette Evaluation Questionnaire[46] will be measured at all contacts (at post-quit contacts this will only be in those who have returned to smoking). We will ask the participant to focus on the cigarette after the evening meal (or equivalent in shift workers). For those who smoke after quit day, we will measure reward from smoking, which might be decreased by preloading. The mCEQ measures satisfaction, taste, mood, cognitive, and sensory sensations to smoking particular cigarettes. At pre-quit contacts we will also use two simple single item rating scales which provided more useful data than the mCEQ in our trial of varenicline preloading [47]. These ask participants to rate 'Have you found your urges to smoke stronger or weaker than usual in the last week' with response options of 'Much stronger, slightly stronger, same as before, slightly weaker, and much weaker'; and 'Have you found cigarettes more or less enjoyable than usual in the last week?' with response options of 'Much more enjoyable, slightly more enjoyable, same as before, slightly less enjoyable, and much less enjoyable'. We hypothesise that preloading would reduce satisfaction and the degree to which it does might be associated with improved outcome.

We will also measure changes in urges to smoke-measured using the urge strength and frequency questions from the Mood and Physical Symptoms

Scale[48] at all contacts. These questions are both strongly correlated with FTND and predict successful smoking cessation more strongly than FTND or other alternatives, such as the Questionnaire of Smoking Urges[49, 50]. Changes in stereotypy- a measure of the degree to which smoking is prompted by cues to smoke- will be measured using a subsection of the Nicotine Dependence Syndrome Scale[51], at baseline and the visit one week after baseline. Only two questions from this scale will be used as the other questions in the scale are either forced to change if cigarette consumption drops or could not be assessed over a short period

Two variables that we do not expect to mediate the relation between preloading and abstinence will be measured. These are confidence in quitting and motivation to quit. They are often presumed to be mediators of smoking cessation success (but the effects are much less than supposed[19]) and we will test this empirically. They are measured by single items only, using standard wording. These are "How high would you rate your chances of giving up smoking for good at this attempt?" and "How important is it to you to stop smoking for good on this attempt?" These variables will be measured at baseline and after the first week of preloading.

Smoking consumption will be assessed at each contact using cigarettes per day- measured using self-report and/or changes in smoke inhalation- measured by change in exhaled CO. This will be used to assess whether consumption reduces pre-quit in either or both arms, and to establish whether relapsed participants smoke fewer than at baseline or return to their previous consumption.

Aversion to smoking will be measured at baseline, the week following baseline, 1 week post-quit, and at 6 and 12 month follow-ups. Interviews with participants taking part in a previous trial[52], where participants were asked to use nicotine patches for 2 weeks whilst still smoking, found that a number of participants thought that preloading worked because it made smoking aversive, for example by creating nausea and/or making a participant lose the will to smoke, which made some keen to quit. Therefore we will test whether participants do find smoking aversive whilst using patches and if so for how long this effect persists. Interview participants' responses suggest that markers of aversion are loss of the will to smoke and nausea. We are already measuring urges to smoke using the Mood and Physical Symptoms Scale[48]. We will measure nausea by asking participants to indicate the extent to which they have experienced nausea in the following circumstances: when they have seen cigarettes, lighters or other smoking paraphernalia, and when they have smelt cigarette smoke. These situations were chosen as they are likely to be applicable to both participants who are smoking and those who are abstinent. Alongside this, at their visit one week after baseline, participants will be asked about the ease with which they

are smoking alongside the patch. After being asked how many cigarettes per day they are smoking participants will be asked: 'Have you had to force yourself to smoke these?', and if so, to what extent? (rated from 'Very much so' to 'Not at all')

We will assess the extent to which participants adhere to the preloading treatment at the visit one week after baseline and one week after quit day. As the time between these two visits will be at least a month participants will be given a simple means with which to record whether they have put their patch on each day. This will not need to be returned to the trial team but can be used by the participants when reporting their adherence to the researcher. Potential side-effects of NRT patch use will also be measured at the contact one week following baseline assessment, and one week post-quit.

These assessments will allow us to examine whether preloading influences the potential mediators which are then responsible for any differences in outcome between the active and placebo groups.

We also plan to use the trial to investigate change in weight in smokers who abstain and those who do not achieve abstinence. It would be ideal to weigh everyone at baseline and throughout treatment to see how weight changes in relation to attain abstinence and relapsing. However, no scheduled in-person follow ups are due during the period when most relapses will take place. For abstinent smokers, it will be possible to get accurate weights at baseline and six and 12 month follow-ups. For non-abstinent smokers, we will have to rely on telephone follow-up and get a self-reported weight at 6 and 12 months. We plan to ask participants at these follow ups to stand on their own scales during the telephone call or to report last weight, both of which are likely to be party to a margin of error. To compensate for this error, we will ask participants to weigh themselves at home prior to attending clinic at baseline and this self-report weight will be recorded along with the calibrated measured weight. The difference between these will be used as a correction to the weights obtained at follow-up. By asking attendees to provide self-reported weight as well as measured weight at follow-up we will be able to calculate the difference again and measure the reliability of the correction. In addition to the measures above at baseline we shall also measure other potential predictors of weight change. We shall measure height using a height measure. Alcohol intake shall be assessed by asking participants about their alcohol intake over a typical week, including the number of alcoholic drinks per week, how large these drinks are, and on how many days of the week the participant usually drinks, in order to allow an estimation of average units per week. We will also ask participants to provide their heaviest weight to date, and measure previous quit attempt weight gain by asking participants how long they were abstinent for at their most

successful (longest) quit attempt, and how much weight they gained during this attempt. We have prepared centile charts of weight gain and the centile chart z-score will be used as the predictor in the modelling. This effectively adjusts for length of abstinence.

At the end of the first week after quit day, participants will be asked about their experiences of preloading. Their response will be recorded by ticking simple emergent categories that apply. These will be based on responses given in a recent interview study conducted as part of the Rapid Reduction Trial[52] and will include categories such as: 'did not feel urge to smoke', 'smoking rate reduced', felt no effect of preloading'. They will also be asked to rate the helpfulness of the intervention, and whether they would recommend it to somebody else by answering the following questions: 'How helpful did you find the preloading intervention?' (answers rated on a scale from 'Very helpful' to 'Not very helpful'), and 'Would you recommend the preloading intervention to somebody else?' ('Yes' or 'No').

We will assess participants' use of health services (including primary and secondary care) during the preloading and follow-up so as to assess whether the intervention might have caused an increase in use (see health economic analyses).

Researchers will obtain saliva samples to measure salivary cotinine concentration at baseline (while smoking only), and one week after enrolment (while smoking on nicotine/placebo patch). Following advice from the funder, funding for the analysis of cotinine samples is not available. We will seek this separately, when the study has been completed. If there is no effect of preloading then analysis of saliva samples will not be beneficial, and so will not proceed. Researchers, trained in phlebotomy, will also obtain blood samples at baseline. DNA will be extracted from these to add to existing databases of genetic information from smoking cessation trials. These samples will not be used for the purposes of the analyses taking place in the current trial, but will be used as part of the larger databases to investigate genetic markers of nicotine addiction and successful cessation as part of separate studies. Previous to cotinine analysis and DNA extraction samples will be stored in locked freezers at each of the trial centres (University of Nottingham, University of Birmingham, Queen Mary, University of London, University of Bristol), in a locked room accessible to the research team. Samples will be identifiable only by trial identification number.

11.2 Loss to Follow-Up

In accordance with the Russell Standard[38], we will conduct an intention to treat analysis, and assume those lost to follow-up are smokers. We will make three attempts to contact participants using their preferred method before an attempt at follow-up is abandoned.

11.3 Trial Closure

The end of the trial is defined as the last date of follow-up of the last patient, and following database lock. However at present there is uncertainty as to when the last follow-up will take place. We will conduct a futility analysis with the aim of saving resources of the funding body (HTA NIHR). The futility analysis will take place 30 months or as soon thereafter when all the primary outcome data are collected. The analysis will examine the difference between arms in the frequency of occurrence of the primary outcome (6 month follow-up data). If there is a lack of significant effect ($p< 0.05$) at 6 month follow-up, then the 12 month follow-up shall be terminated and the study will close at 36 months after commencement. If there is a significant difference in 6 month abstinence then 12 month follow-up will be completed, taking the study to 42 months duration.

12 STATISTICS AND DATA ANALYSIS

12.1 Sample size

This is determined based on plausible estimates of the six month confirmed prolonged abstinence rate in the control group and the efficacy of preloading. A recent trial showed a six month abstinence rate of 15%.[53] Another as yet unpublished trial of 631 participants also found a similar prolonged abstinence rate.[54] We have therefore settled on an abstinence rate in the control group of 15%. Our meta-analysis found summary RRs of 1.05 for short-term and 1.16 for prolonged abstinence[8]. However, there was heterogeneity, perhaps explained by use/non-use of the patch, but other differences between trials make this uncertain. It is therefore difficult to settle on a specific RR, but we chose 1.4 as plausible and an effect likely to interest the NHS stop smoking services. The RR (95%CI) for abstinence in the patch trials, in our review[8], was 1.17 (1.00, 1.37) for short-term and 1.26 (1.03, 1.55) for long-term abstinence, but with unexplained heterogeneity, so our RR appears reasonable. For example an RR of 1.4 means that the summary effect for NRT is about 2.2, similar to that for varenicline versus placebo (2.3)[3]. This gives us a sample size of 893/arm or 1786 in total for 90% power (See Table 3).

12.1 Analysis Plan

The primary analysis will be performed using the full (intention to treat) dataset, including all those randomised, presuming that those who do not provide data at follow-up are continuing to smoke. We will compare the proportion of people achieving the primary outcome using the risk ratio and the difference in proportions, calculating 95% confidence intervals. These figures allow clinicians to have an intuitive sense of the size of the effect. However, the primary effectiveness analysis will be based on an adjusted odds ratio, calculating first an unadjusted odds ratio (for comparison), and then an adjusted OR. We will adjust for two prognostic factors to improve the precision of the treatment effect

estimate: length of previous abstinence achieved and baseline urges to smoke (using the urges questions from the MPSS), which have both been shown to be predictors of success[49, 50, 55], using multiple logistic regression in Stata. In sensitivity analysis, we will also adjust for post-cessation medication use, because varenicline is more effective and this might be imbalanced. Secondary outcomes will be analysed similarly. A p value of <0.05 will be considered statistically significant. We will calculate the proportion of people finding the intervention helpful, but not compare these between arms with inferential statistics.

Table 3: Sample size for 80% and 90% power for different combinations of control and intervention prolonged abstinence rates (calculated with Yates correction using nQuery

		Trial with 80% power	Trial with 90% power
% prolonged abstinence in control	% prolonged abstinence in intervention	Number/arm	Number/arm
RR=1.3			
14	18.2	1249	1655
15	19.5	1150	1524
16	20.8	1064	1409
20	26	805	1065
RR=1.4			
14	19.6	734	970
15	21	676	893
16	22.4	625	825
20	28	471	622
RR=1.5			
14	21	490	646
15	22.5	451	594
16	24	416	549
20	30	313	412

The safety analysis will be performed on all participants who complete follow-up at 1 week following baseline or follow-up one week after quit day. We will examine the occurrence of moderately and severe adverse events as a group and serious adverse events. We will also code events using the MedDRA coding database to examine the specific problems that might occur with preloading. We will relate these to baseline characteristics and changes in smoking behaviour to examine for predictors of adverse events. The analysis will be performed in Stata using logistic regression.

The mediation analysis will proceed using the procedure outlined by MacKinnon using regression modelling.[56] We will estimate the mediated effect using mediation regression equations, modelling the association between abstinence (dependent variable) and intervention, and between abstinence

(dependent variable), the intervention and the potential mediators, in both cases using logistic regression, and between (continuous) mediators and the intervention using linear regression. The mediated effect will be estimated by the product of coefficients method, using the appropriate coefficients from the regression models, and using bootstrapping to compute confidence limits of the mediated effect. We also propose a two step mediation process whereby preloading leads to higher nicotine concentration (reflected by cotinine concentration) which in turn leads to reduction in measures of dependence that lead to improved abstinence. We will examine this using Mplus with a structural equation model.

We will conduct exploratory subgroup analyses to examine whether the effect of preloading is similar for people who use varenicline or those using NRT, first testing for effect modification with a multiplicative interaction term in logistic regression. (We expect the proportion using bupropion to be small). Similarly we will examine whether the effect of preloading is modified by dependence level (assessed by FTND, exhaled CO, and salivary cotinine), demographic characteristics, previous use of pharmacotherapy to quit and smoking history. We will also investigate the proportions of reactors and non-reactors to the preloading treatment (those who do/do not experience reductions in CO, cigarettes per day and cigarette reward, between baseline and the visit 1 week following this), whether quit rates differ between these two groups, and whether this is modified by the pharmacotherapy participants are provided with from the NHS SSS.

Our first question on weight is whether smokers who become abstinent and gain weight lose it again at follow-up. As most people who relapse will do this prior to 6 month follow up, we will have no contemporaneously collected data on weight attained and therefore cannot examine whether weight was lost. Instead we will approach this indirectly by comparing weight change in people who are relapsed at follow up to population weight gain norms. Weight gain depends upon gender, age, and body mass index, so for each individual we will calculate an expected weight change using data from a meta-analysis of cohort studies.[57] We will then calculate the difference between observed and expected weight gain, and the mean of these differences for abstinent and non-abstinent participants will be calculated and compared to an expected difference of 0kg using a one-sample t-test and compared with each other in a two-sample t-test. This analysis will show whether smokers who become abstinent gain more weight than expected, but this is well established. Less established is what happens to smokers who gain weight but relapse. If their weight gain is greater than expected from population norms, this might suggest that unsuccessful attempts to stop smoking are associated with incremental weight gain, which

would imply that abstinent smokers who relapse do not lose the weight that they gained during the quit attempt. We will explore this in two further analyses.

First, we aim to calculate the expected weight gain for relapsed smokers assuming that they do not lose weight on relapse. We can calculate the expected weight gain for each month of abstinence from a meta-analysis of cohort studies of weight gain after abstinence[25]. We will add this to the expected weight gain when not abstinent from a meta-analysis of cohort studies of the general population[57]. If weight is not lost, then the mean observed and expected weight gain will be similar and we will examine this using a one-sample t-test. We will also use a regression equation to examine weight change in relation to length of abstinence adjusting for age, gender, and baseline BMI. We will use length of abstinence categorised by dummy variables for months of abstinence achieved to allow for a non-linear relation.

The second aim relating to weight gain is to create a predictive model that could be used to differentiate people who are at low risk of weight gain if they become abstinent from those who are at higher risk (to be able to offer the latter special interventions). To do so we will use data collected routinely in smoking cessation clinics plus alcohol consumption, which is not routinely collected in these settings but is so in primary care. The modelling will use measured weight in abstinent smokers only assessed at six and 12 months, with separate models for each. Excess weight will be defined as more than 4kg at 6 months and 5kg at 12 months, which is about the median weight gain at these times. We will investigate the effects of varying the threshold. Using logistic regression with backwards elimination with $p<0.05$ we will investigate the predictors of weight gain using baseline cigarette consumption, FTND (noting the potential for collinearity), age, gender, baseline BMI, socio-economic status, educational qualification, ethnicity and alcohol consumption. We will construct a receiver operating characteristic curve to assess the ability of the model to differentiate people at higher risk from those at lower risk and assess the optimum cut-points for these. The data would need confirmation in a separate replication sample, but could easily be incorporated into a simple tool akin to the Framingham score.

Cost-effectiveness analysis

Cost-effectiveness analysis will be conducted by combining data collected within the trial and existing models. We will calculate the proportion of prolonged abstinent participants produced by the intervention. We will estimate the costs of the behavioural support and NRT using a similar approach adopted in our previous HTA reports/economic modelling [58, 59], using local costings where appropriate. These models will enable the calculation of the proportion of lifetime quitters, the cost/lifetime quitter, the cost/life year gained and the cost/quality adjusted life year. We will compare the health service use for the

active and placebo groups to assess whether preloading leads to extra health service use. Longer term NHS costs can be estimated using a cost model recently developed by the PHRC involving one of the investigators [60]. Cost effectiveness acceptability curves will be used to demonstrate the value for money based on a range of threshold values for a QALY.

12.2 Data Handling, Record Keeping and Retention

The trial is being run as part of the portfolio of trials in the Primary Care Clinical Trials Unit (PC-CTU), a National Institute for Health Research (NIHR) recognised trials unit in Primary Care Health Sciences at the University of Oxford. The data management will be run in accord with the standard operating procedures, which are fully compliant with the Data Protection Act and Good Clinical Practice (GCP). The source documents for the trial will be the case report forms which will be stored in the trials unit in a locked cabinet in a locked office in a locked department. These will be transferred from the site of the research visits to the universities personally by the researchers, and consent will explicitly be sought from participants to do so. The trial database will be securely developed, held and maintained by the PC-CRTU at the University of Birmingham. On completion of the trial and data checking, the case report forms will be transferred to a secure, GCP compliant, external archiving facility, where they will be held for 15 years and then destroyed. The database will be anonymised and a secure compact disc containing the link between identification number and patient identifiable information will be stored in a secure archiving facility.

12.3 Data Access and Quality Assurance

Data will be kept in accordance with the Data Protection Act. The standard operating procedures of the trials unit will be followed, which are designed to protect patient confidentiality. Patient identifiable data will be shared only within the clinical team on a need-to-know basis to provide clinical care and ensure good and appropriate follow up. Patient identifiable data may also be shared with the general practitioner and approved auditors from the Research Ethics Committee, NHS Research and Development, or the Medicines and Healthcare Regulatory Authority will also be able to see patient identifiable information. Otherwise, confidentiality will be maintained and no one outside the trial team will have access to either the case report forms or the database.

12.4 Case Report Forms

The secure online database used for trial ID allocation and randomisation will incorporate an online case report form (CRF). There will however also be a paper copy of CRFs. This is because the CRF will need to be completed to correspond with each clinic visit/follow-up, however there may not always be access to a computer or internet connection when trial clinics are taking place. In this case the paper CRF will be completed and data will be copied to the online version at

a later date. As previously mentioned paper CRFs will be kept in a locked cabinet in a locked office in a locked department.

13 SAFETY MONITORING PLAN

13.1 Risk Assessment

A risk assessment has been carried out in accordance with MHRA guidance on Risk Adapted Approaches to Monitoring. A suitable monitoring plan will be drawn up and appropriate on-site and central monitoring will be performed.

13.2 Monitoring at Study Co-ordination Centre

The trial will be conducted in accordance with the risk assessment, monitoring plan, current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

Monitoring will be performed by the University of Oxford's Clinical Trials and Research Governance (CTRG) Office according to CTRG SOPs and ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

Data cleaning will take place by a series of logical checks on the electronic data. (For example, a person cannot be recorded as prolonged abstinent smoker at 6 months if they were not in such a state at 4 weeks). Discrepant records will be checked with the source documents and the database amended if necessary.

The trial may be subject to monitoring by the lead Comprehensive Local Research Network. Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. Therefore participants will be asked for consent to allow their records to be viewed by these authorities.

13.3 Monitoring At Local Site

The monitor will perform site visits, the team will be trained in all aspects of the protocol and trial procedures and the monitor will check this as a part of their visit (compliance to protocol and delegation logs and CVs).

14 SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial".

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the NHS host organisation within seven calendar days.

15 REGULATORY ISSUES

15.1 Clinical Trial Authorisation (CTA)

This study has Clinical Trial Authorisation from the UK competent authority (MHRA)

15.2 Ethics Approval

The Study Co-ordination Centre has obtained approval from the NRES Committee East Midlands - Leicester (REC Reference: 12/EM/0014).

15.3 Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

15.4 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

15.5 Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, host organisation and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

15.6 Patient Consent

The process for obtaining participant informed consent will be in accordance with Good Clinical Practice (GCP). The researcher and the participant shall both sign and date the consent form before any trial procedures begin.

A copy of the signed form will be kept by the participant, and the original will be retained in the appropriate site file. Another copy will be forwarded to the GP to file in the participant's medical notes.

The participant's decision to take part in the trial is entirely voluntary. It will be explained to potential participants that they can withdraw consent at any time without penalty or affecting the quality or quantity of their future medical care.

Participants will be informed of any relevant information that becomes available that affects their participation in the study. Revised consent forms will be used if applicable, and amended forms will be submitted to the main REC for favourable opinion prior to use. Revised informed consent forms will be signed by the parties specified above.

15.7 Confidentiality

Participants' identification data will be required for the registration process. The study co-ordination centre will preserve the confidentiality of participants taking part in the trial, and is registered under the Data Protection Act. Confidentiality will be monitored, and consent will be sought from patients for members of the study team, regulatory authorities and the relevant PCT to have direct access to patient medical records.

15.8 Indemnity

The University of Oxford has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London, policy numbered :WD1200463). NHS indemnity operates in respect of any clinical treatment which is provided.

15.9 Sponsor

The University of Oxford will act as the sponsor for this trial.

15.10 Funding

The National Institute for Health Research Health Technology Assessment programme is funding this trial.

15.11 Audits

The trial may be subject to inspection and audit by The University of Oxford under their remit as sponsor, the study co-ordination centre and other regulatory bodies, such as The Medicines and Healthcare Regulatory Agency to ensure adherence to GCP.

16 FINANCIAL ARRANGEMENTS

16.1 Participant Payments

Participants will receive payment for travel and inconvenience at the following visits:

1 week post enrolment - £15 to intervention and control groups
6 months clinic follow up - £15 to intervention and control groups
12 months clinic follow up - £15 to intervention and control groups

16.2 GP Payments

No payments will be made to GP Surgeries or NHS Stop Smoking Service providers, aside from NHS service support costs, as agreed with the PCRN.

17 PUBLICATION

All publications and presentations relating to the trial will be authorised by the trial steering committee. Named authors will include at least the chief investigator, statistician (if relevant to content) and trial co-ordinator. Members of the trial steering committee will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy.

TRIAL PERSONNEL CONTACT SHEET

Brief Study Title: RCT of Nicotine Preloading for Smoking Cessation

Study Start Date: 1 January 2012

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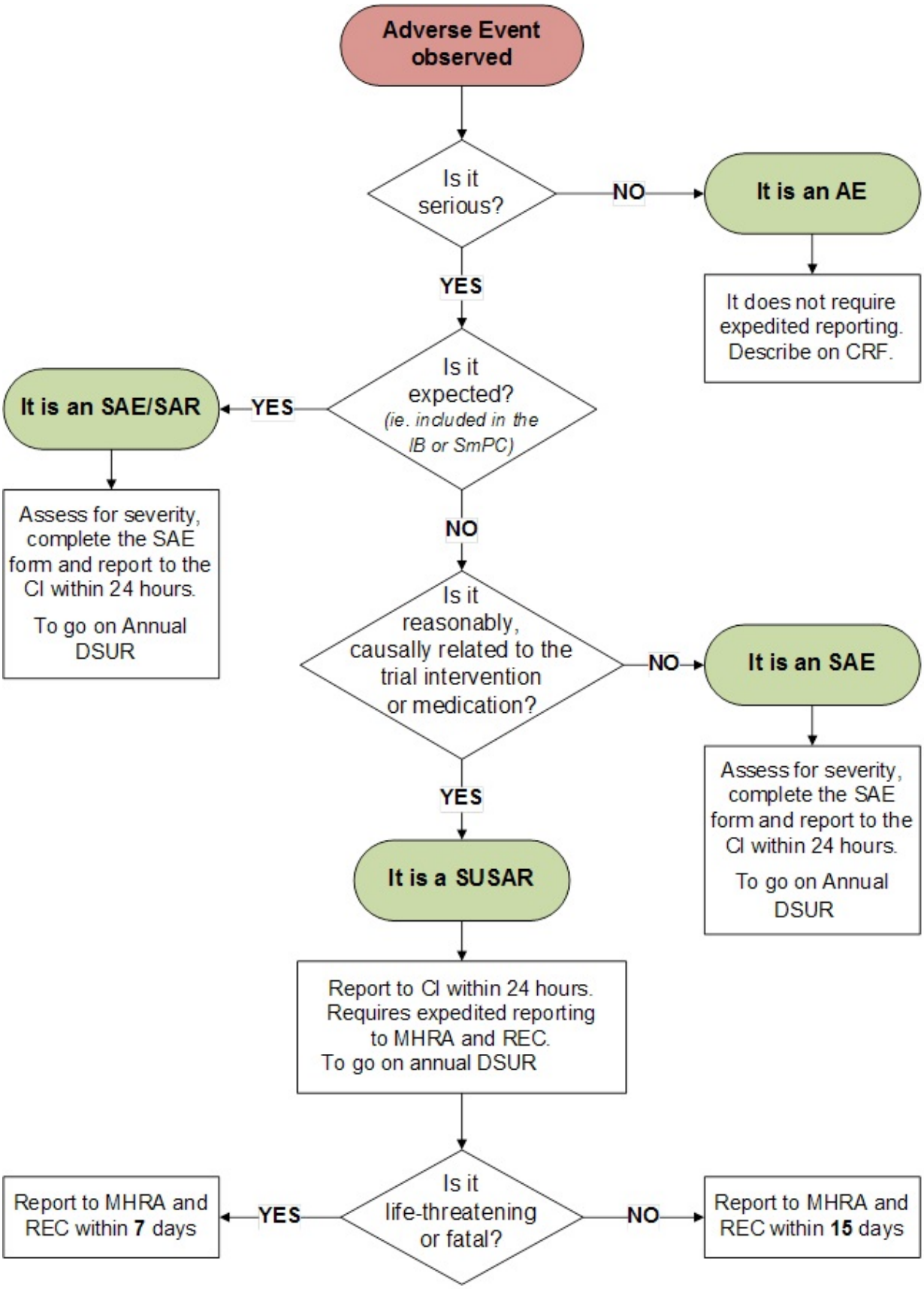
PHARMACOVIGILANCE FLOWCHART



Study Sites

West Midlands:
South Birmingham PCT
Sandwell PCT,
Birmingham East & North PCT
Solihull PCT
Dudley PCT
Warwickshire PCT
Worcestershire PCT
Birmingham Community Healthcare NHS Trust
University of Birmingham (non-NHS)

Bristol:
Bristol PCT

London:
East London Stop-Smoking Service clinic (non-NHS), funded by Tower Hamlets and City & Hackney PCTs)

Nottingham:
Nottinghamshire County Teaching PCT
Nottingham City PCT
Derby City PCT
Derbyshire County PCT

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