Primary Care Clinical Trials Unit

STATISTICAL ANALYSIS PLAN

Examining the effectiveness of general practitioner and nurse promotion of electronic cigarettes versus standard care for smoking reduction and abstinence in hardcore smokers with smoking-related chronic disease: a randomised controlled trial

Short title: Management of smoking in primary care (MaSC)

Version 1.0

10th March 2020

Based on version 3.0 of Protocol (7th May 2019)

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1 INTRODUCTION

1.1 PREFACE

The chief investigator of the trial is Rachna Begh (RB). The trial statistician is Nicola Williams. The data manager is Jenna Grabey. Other investigators are Paul Aveyard, Rebecca Barnes, Tim Coleman, Hazel Gilbert, Felix Naughton, Lucy Yardley, Anne Ferrey and the MaSC trial team.

The investigators and statisticians produced the research protocol (version 3.0) and all CRFs. This statistical analysis plan (SAP) (version 1.0) was written by Rachna Begh and reviewed by Nicola Williams. It supports version 3.0 of the research protocol, dated 7th May 2019. All analyses will be performed using a current version of STATA.

1.2 PURPOSE AND SCOPE OF THE PLAN

The purpose of this statistical analysis plan is to set out the study objectives, and the analytical approaches and procedures necessary to address these. The qualitative analysis of interviews and audio recordings are not covered here.

This document details the proposed analysis of the main paper(s) reporting results from the NIHR Postdoctoral Fellowship and NIHR School for Primary Care Research funded randomised controlled trial exploring the effectiveness of GP/nurse promotion of e-cigarettes in supporting reduced smoking and abstinence in hard-core smokers with smoking-related chronic disease. The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged. Any deviations from the statistical analysis plan will be described and justified in the final report of the trial.

The plan draws on statistical guidance ICH Guidance on Statistical Principles for Clinical Trials, the CONSORT statement for reporting trials and PC-CTU statistical SOPs.

1.3 TRIAL OVERVIEW

Despite the clear harm associated with smoking tobacco, many people with smoking-related chronic diseases are unwilling or unable to stop smoking. In many cases, these smokers have tried and exhausted all methods to stop smoking and yet clinicians are repeatedly mandated to offer them during routine consultations. Providing nicotine through electronic cigarettes (e-cigarettes), may reduce the adverse health consequences associated with tobacco smoking, but these are not currently offered. The aim of this study is to examine the feasibility, acceptability, and effectiveness of general practitioners and nurses delivering a brief advice intervention on e-cigarettes and offering an e-cigarette starter pack and patient support resources compared with standard care in hardcore smokers unwilling to stop smoking.

1.4 OBJECTIVES

Primary objectives

The primary objective is to examine the effectiveness of a brief GP/nurse behavioural intervention to encourage switching to e-cigarettes, provision of e-cigarettes, and ongoing technical support from experienced e-cigarette users in producing short-term reductions in cigarette intake and smoking abstinence.

Secondary objectives

The secondary objectives are:

- To examine recruitment and follow-up of patients.
- To examine smokers' uptake and use of offered e-cigarettes.
- To assess contamination of randomisation.
- To examine nicotine intake.
- To assess the fidelity of primary care teams in delivering brief interventions.
- To examine practitioners' reactions towards offering e-cigarettes and experiences of delivering the intervention.
- To examine patients' reactions to the programme.
- To examine the vape team's reactions towards supporting patients in their use of e-cigarettes.
- To examine the effectiveness of a GP/nurse-led brief intervention for smoking on long-term reductions in cigarette intake and smoking abstinence.

2 TRIAL DESIGN

This is a two-centre, individually randomised, two-arm, parallel group study. The study will take place in general practices in England. A total of 320 smokers with a smoking-related chronic disease and who have no intention of stopping immediately or seeking cessation support will be randomised to one of two groups, if they decline referral to NHS stop smoking services (SSS) and smoking cessation medication: an intervention group offered encouragement by their practitioner to use an e-cigarette, or a standard care control group who will receive nothing beyond the usual care already provided prior to randomisation. Participants in the intervention group will be offered an e-cigarette starter pack and accompanying practical support booklet; this will contain details for a telephone call back service run by experienced vapers for technical support and a website with an online video tutorial.

Due to the nature of the trial, GPs and practice nurses will be aware of the patient's treatment allocation to ensure that the correct intervention is given. Therefore, practitioners who are delivering the intervention cannot be blinded to treatment. While patients will know whether they have been offered support to cut down by using an e-cigarette or not by their GP or nurse, the patient will not be informed that this study is investigating this specifically and therefore will in some respects remain blind to allocation.

Patients will attend four visits at their GP practice: a baseline visit, a therapeutic visit ('annual review') with their GP or nurse and two follow-up visits two months and eight months post-consultation.

2.1 OUTCOMES MEASURES

List of outcome measures by timepoint is in Appendix 1.

Primary outcomes

2.1.1 PRIMARY OUTCOME

Primary outcome measures are:

- 7-day point-prevalence abstinence from smoked tobacco at two months, defined as complete self-reported abstinence from smoking – not even a puff – in the past seven days, accompanied by a salivary anabasine concentration of <1ng/ml. If there are technical issues with the analysis of saliva

samples (e.g. if there is not enough saliva present in the sample for anabasine analysis), we will use exhaled CO as verification of abstinence (CO <10 ppm).

- Reduction in cigarette consumption at two months, defined as at least a 50% reduction in self-reported cigarettes per day on each of the last seven days at two months compared with baseline consumption, accompanied by evidence of reduced smoke intake indicated by a CO measurement lower than baseline.

2.1.2 SECONDARY OUTCOMES

2.1.2.1 EFFICACY OUTCOMES

Secondary outcome measures are:

- 7-day point prevalence abstinence measured at eight months, biochemically confirmed by an exhaled CO of <10 ppm.
- Six-month prolonged abstinence using the Russell standard criteria, defined as smoking fewer than five cigarettes between two and eight month follow-ups, confirmed by an anabasine concentration of <1ng/ml at two months and an exhaled CO concentration of <10ppm at eight months (or anabasine concentration of <1ng/ml at eight months if CO measurement unavailable).
- Mean change in salivary anabasine concentration from baseline to two months.
- Mean change in CO values from baseline to two months.
- Percentage reduction in self-reported cigarettes per day from baseline to two months.
- Percentage reduction in self-reported cigarettes per day from baseline to eight months.

2.1.2.2 NON-EFFICACY OUTCOMES

1. Recruitment and follow-up of patients

   This outcome will be measured by recording:

   - The number of people in the population of interest who respond to letters of invitation from the practices.
   - The number of people who consent to enrolment into the study at baseline.
   - The number of people who complete follow-up at two months after receiving the brief advice intervention.
   - The number of people who complete follow-up at eight months after receiving the brief advice intervention.

2. Patient uptake and use of e-cigarettes

   Patient uptake of the offer of an e-cigarette will be assessed by:

   - The practitioner recording on the randomisation card at the annual review appointment, with a question that asks whether an e-cigarette starter pack was accepted or declined by participants (yes/no binary variable).

   Use of offered e-cigarettes at two month follow-up will be assessed by patient questionnaire in the following way:

   - The total number of times the e-cigarette was used per day or weekly (i.e. 'sessions' not puffs).
   - The length of time using the e-cigarette (months, weeks and days).
   - The brand of e-cigarette.
   - Strength of nicotine e-liquid.
   - The e-liquid flavours used.

- The ten item Electronic Cigarette Dependence Index (ECDI) as a measure of e-cigarette dependency.

Use of offered e-cigarettes at eight month follow-up will be assessed by patient questionnaire in the following way:

- The total number of times the e-cigarette was used per day or weekly (i.e. 'sessions' not puffs).
- The length of time using the e-cigarette (months, weeks and days).
- The brand of e-cigarette.
- Strength of nicotine e-liquid.
- The e-liquid flavours used.
- The ten item Electronic Cigarette Dependence Index (ECDI) as a measure of e-cigarette dependency.

3. Contamination of randomisation
   Contamination, defined as e-cigarette advice and/or the offer of an e-cigarette given to control group participants - will be assessed in the post-consultation questionnaire in the following way:
   - Control group participants will be asked to report on whether e-cigarettes and other smoking cessation aids were mentioned during the consultation (yes/no binary variable). If e-cigarettes were mentioned, we will verify the response against available audio recordings of the consultation. If there is a discrepancy between the self-reported data and audio recording, we will make a correction based on the audio recording.

4. Nicotine intake and nicotine (cigarette) dependence
   - Nicotine intake will be measured to examine whether participants in the intervention group cut down or replace their nicotine intake with e-cigarette use. This will be measured by analysing cotinine concentrations in saliva samples taken at baseline and two month follow up.
   - Severity of cigarette dependence at two months, using the six-item Fagerstrom Test for Cigarette Dependence (FTCD).
   - Severity of cigarette dependence at eight months, using the FTCD.

5. Fidelity
   Adherence of primary care teams in delivering brief interventions will be assessed using a study-specific behaviour checklist. The checklist will examine adherence across three domains: eligibility, delivery of usual care and delivery of the intervention.
   - Eligibility
     - Whether the practitioner randomised the patient and their reasons for not doing so. This will be verified against audio recordings of the consultation to examine whether the practitioner should or should not have randomised the patient (yes/no binary variable) according to our inclusion and exclusion criteria. If there is a discrepancy between the practitioner's self-reported reasons for exclusion and the audio recording, we will make a correction based on the audio recording.

   - Delivery of usual care
     - Whether the practitioner asked the participant about their smoking status (yes/no binary variable). This will be assessed from the audio recording of the consultation only
     - Whether the practitioner gave brief smoking management and cessation advice (yes/no binary variable). This will be assessed from the audio recording of the consultation only

- Whether the practitioner offered a referral to the stop smoking services or offered smoking cessation treatment (yes/no binary variable). This will be assessed from the audio recording of the consultation only.

- Delivery of intervention (in intervention group only)
- Whether the practitioner advised their patient about e-cigarettes (yes/no binary variable), verified against the audio recording of the consultation
- Whether the practitioner offered the patient an e-cigarette starter pack (yes/no binary variable), verified against the audio recording of the consultation
- Whether the patient accepted the e-cigarette starter pack (yes/no binary variable), verified against the audio recording of the consultation.

6. Practitioners' knowledge and attitudes towards offering e-cigarettes
   Before intervention training begins and after all therapeutic visits have been completed at a practice, practitioners will be given a questionnaire about their attitudes regarding e-cigarettes as a tool for smoking cessation, as a measure of self-efficacy and outcome expectations.

- Self-efficacy
  Four items measure self-efficacy: "How comfortable are you about advising your patients to switch from cigarettes to e-cigarettes?"; "I have sufficient knowledge to offer brief advice about e-cigarettes"; "I have enough confidence to give patients advice on e-cigarettes"; "I am able to convey the benefits and risks of e-cigarettes in a balanced way to patients".

- Outcomes expectancies
  Two items measure outcome expectancies: "How helpful do you think e-cigarettes are for encouraging people to reduce their smoking and quit?" and "How likely is it that brief advice and an offer of an e-cigarette from you would motivate your patients to try an e-cigarette?"

  All items are rated and coded from 1 to 5 (1 = not at all, 5 = very much). For each question the difference between their pre and post-trial responses will be computed.

  Practitioners and the vape team's experiences of the programme are also explored via qualitative interviews, the analysis for which is described in the protocol and not detailed here.

7. Patient acceptability of the intervention
   Participants' reactions to the practitioner discussing smoking will be measured by two post-consultation questions immediately after the annual review consultation. This will assess:
- How helpful participants found the practitioners' advice and support on smoking. Each question has 5 possible responses, which are values 1 to 5, with 1 indicating the most negative response and 5 indicating the most positive response.
- How appropriate participants found the practitioners' advice and support on smoking. Each question has 5 possible responses, which are values 1 to 5, with 1 indicating the most negative response and 5 indicating the most positive response.

  We will assess attitudes towards e-cigarettes, cutting down and stopping smoking in a questionnaire administered at baseline and two months, as a measure of self-efficacy and outcome expectations.

- Self-efficacy
  Four items measure self-efficacy: "It's easy for me to stop smoking"; "It's easy for me to cut down on my smoking"; "I know how to set up and use an e-cigarette"; and "I know how to purchase e-liquids and replacement cartridges/coils for an e-cigarette".

- Outcome expectancies

Two items measure outcome expectancies: "I think e-cigarettes are less harmful than cigarettes" and "I could enjoy e-cigarettes as much as cigarettes". All items are rated and coded 1-5 from "Strongly Disagree" to "Strongly Agree".

All items are rated and coded from 1 to 5 (1 = not at all, 5 = very much). For each question the difference between their pre and post-trial responses will be computed.

For intervention group participants only at the two month follow-up, we will assess:

- Whether participants reported that they were contacted by an experienced e-cigarette user when they first received their e-cigarette (yes/no binary) and if so, how helpful they found the advice offered, measured on a five-point Likert scale from "Very unhelpful" to "Very helpful", coded 1-5.
- Whether participants reported that they contacted the vape team (yes/no binary) and if so, how helpful they found the advice offered, measured on a five-point Likert scale from "Very unhelpful" to "Very helpful", coded 1-5.
- Whether participants read the practical support booklet (yes/no binary) and if so, how helpful was it on a five-point Likert scale from "Very unhelpful" to "Very helpful", coded 1-5.
- Whether the participants accessed the study website that featured the online video tutorials (yes/no binary) and if so, how helpful was it on a five-point Likert scale from "Very unhelpful" to "Very helpful", coded 1-5.

2.2 TARGET POPULATION

Participants are able to participate if they are ≥ 18 years of age, a current smoker with a value of at least 10 parts per million (ppm) for exhaled carbon monoxide (CO) and smokes a minimum of 8 cigarettes/8 grams of tobacco per day (including pipe, cigars or tobacco roll-ups) and diagnosed with one or more of the following chronic conditions as defined in the QOF: ischaemic heart disease, peripheral vascular disease, hypertension, diabetes mellitus (Type 1 and Type 2), stroke, asthma, COPD, chronic kidney disease, depression, schizophrenia, bipolar disorder or other psychoses.

The patient may not enter the trial if any of the following apply: (1) GP believes that switching to e-cigarettes would not benefit the patient given their current medical condition; (2) Currently using e-cigarettes, nicotine replacement therapy or other cessation therapies (e.g. bupropion, nortriptyline or varenicline); (3) Plans to stop smoking before or at the annual review (4) Currently enrolled in another smoking-related study or other study where the aims of the studies are incompatible; (5) Cannot consent due to mental incapacity; (6) Pregnant, breastfeeding or planning to become pregnant during the course of the study.

2.3 SAMPLE SIZE

We aim to recruit 320 participants in total. In order to correct the type 1 error rate for the fact that there are two primary outcomes we will be using the Holm-Bonferroni method of adjustment [1]. The smaller P-value will be compared to an alpha of 0.025 (this will probably be for reduction in smoking) and if this is significant, the larger P-value (which will probably be for cessation), will be compared to an alpha of 0.05. A total sample size of 320 will allow us to detect a risk ratio of 2.8 for the proportion of patients reducing their smoking and a risk ratio of 3.4 for the proportion of patients who stop smoking [2]. This assumes power of 90% and control group rates of 5% and 8% for stopping and reducing respectively [2]. No allowance will be made for loss to follow up as all such cases will be assumed to have continued their baseline level of smoking.

We expect to see adherence to the behavioural intervention by practitioners of 70%, use of the e-cigarette at follow-up of 40%, and follow-up 70% of enrolled participants. We will be able to estimate these proportions with 95% confidence intervals being no greater than+/-8% with a sample of 160 people in the intervention group, and +/- 6% for the whole sample of 320 participants.

2.4 RANDOMISATION AND BLINDING IN THE ANALYSIS STAGE

Participants will be randomised to intervention or control with a 1:1 allocation ratio. A randomisation list will be generated by the trial statistician using the current version of Stata and validated by a second statistician within the Primary Care Clinical Trials Unit (PC-CTU). The randomisation will be stratified by practice and will use varying block sizes to ensure allocation concealment. The randomisation list will then be passed to someone independent of the trial who will create the randomisation envelopes. The trial statisticians will be blinded to the treatment allocation during analyses.

3 ANALYSIS – GENERAL CONSIDERATIONS

3.1 DESCRIPTIVE STATISTICS

3.1.1 CHARACTERISTICS OF PARTICIPANTS

The trial sample population will be characterised in terms of diseases of interest that makes them eligible (including comorbid psychiatric conditions), age, gender, ethnicity using UK census 2015 categories, educational qualifications and occupation. For ethnicity categories, if there are cells with zero or small counts, adjacent categories will be combined. Information on smoking history will be reported including age when started smoking, number of cigarettes smoked per day, time since last cigarette smoked, type of cigarettes smoked per day (roll-ups or factory-made), usual pack/pouch size, exhaled CO measurement and nicotine dependence as measured by the six-item Fagerstrom Test for Cigarette Dependence (FTCD). We will report motivation to stop smoking using the question "How likely are you to quit smoking within the next six months?" Responses will be measured on a five-point Likert scale from "Very unlikely" to "Very likely" (scored 1-5). We will report history of any pharmacotherapy or e-cigarette use (yes/no binary variable). A table of baseline characteristics will be produced to show the degree of comparability between participants in the two arms. All data will be summarised by treatment group. For baseline characteristics a total overall column will be included to summarise all participants. Summary descriptions for continuous measurements will be means and standard deviations. Medians and interquartile ranges will be also presented if more appropriate. Proportions will be presented for categorical variables.

No formal statistical testing will be applied to test for any difference between randomised groups with respect to the baseline characteristics and no confidence intervals will be presented.

Patient flow from screening through randomisation, follow up and analysis will be presented in a CONSORT flow chart (Appendix II).

3.1.2 CIGARETTE EQUIVALENTS

At each time-point, participants report the average number of manufactured cigarettes smoked per day, the number of roll-ups *or* grams of tobacco smoked, cigars and pipe sessions. For the assessment of cigarette consumption, the cigarette equivalents for roll-ups, grams of tobacco, cigars and pipe sessions will be calculated.

A new variable will be created for cigarette consumption and will be used in the primary and secondary analyses below based on the following:

- Roll-ups
  1 roll-up = 1 manufactured cigarette

- Grams of tobacco
  1 gram = 1 cigarette

- Cigars

Although we have not measured size of cigar, we know that the smallest cigar size is the equivalent of 1.5 cigarettes and so 1 cigar = 1.5 cigarettes. Taken from http://www.smoking2.nes.scot.nhs.uk/module4/working-out-cigarette-equivalents.html.

- Pipe sessions
  One bowl (defined here as session) of tobacco is roughly equivalent to 2.5 cigarettes (e.g. 8 sessions = 20 cigarettes). Taken from http://www.smoking2.nes.scot.nhs.uk/module4/working-out-cigarette-equivalents.html.

3.2 Definition of population for analysis

The intention-to-treat (ITT) population is defined as all randomised participants i.e. where the practitioner opens the randomisation envelope, and according to the Russell Standard [3] where participants lost-to-follow up are assumed to be smokers or not to have reduced. The Russell Standard also allows removal of people who have died or genuinely moved away. The primary analysis will be ITT with baseline observation carried forward (BOCF). Participants will be summarised according to the treatment to which they were randomised, regardless of which treatment they actually received.

3.3 Pooling of investigational sites

About 30 practices will be recruited for the trial with an average of 11 participants per practice. The data collected are intended to be analysed as a whole but in common with good practice, the analyses described below will be adjusted for the stratification factor, which is individual GP practice.

3.4 Comparison of losses to follow-up and withdrawal

Recruitment, randomisation and follow-up will be summarised in a CONSORT flow-diagram which includes reasons for withdrawal from the trial. See Appendix 2 for participant disposition. Number of patients who were screened for inclusion and were randomised will be presented, as well as number of patients included in the analysis of the primary outcome.

3.5 Data Monitoring Committee And Interim Analyses

There is no DMC for this trial. No formal interim analyses are planned for this trial.

3.6 Statistical methods

As there are 2 primary outcomes, the Holm-Bonferroni method will be used to correct the type 1 error rate. This means that the smaller of the two P-values for the primary outcomes will be compared to an alpha of 0.025. If this is significant, the larger P-value will be compared to an alpha of 0.05.

P-values for all secondary outcomes will be compared to an alpha of 0.05 and treatment effects will be presented with 95% confidence intervals.

4 PRIMARY ANALYSIS

4.1 Primary outcome

4.1.1 Hypotheses

The analysis of the primary outcomes (7-day point-prevalence abstinence from smoked tobacco at two months and a ≥ 50% reduction in average number of cigarettes per day in last 7 days at two months compared to baseline) will be based on the following hypothesis test:

Null hypothesis

Abstinence outcome: there is no difference in the proportion of participants who achieve abstinence at two months between the intervention and the control group, having adjusted for GP practice.

Smoking reduction outcome: there is no difference in the proportion of participants who achieve smoking reduction (i.e. ≥ 50% reduction in average number of cigarettes per day in last 7 days at two months compared to baseline) between the intervention and the control group, having adjusted for GP practice.

Alternative hypothesis

Abstinence outcome: there is a difference in the proportion of participants who achieve abstinence at two months between the intervention and the control group, having adjusted for GP practice.

Smoking reduction outcome: there is a difference in the proportion of participants who achieve smoking reduction (i.e. ≥ 50% reduction in average number of cigarettes per day in last 7 days at two months compared to baseline) between the intervention and the control group, having adjusted for GP practice.

4.1.2 Definitions and derived variables

4.1.2.1 Smoking Cessation

The achievement of 7-day point prevalence abstinence is assessed by means of the participant's self-reported smoking status at the two month follow-up. Self-reported abstinence at two months is verified by a salivary anabasine concentration of <1ng/ml, or in cases where saliva analysis is unavailable or unusable, by CO verification where CO <10 ppm. This is a derived binary outcome and the variable will be coded as yes/no.

Abstinence = 1 (yes) if the participant has reported no manufactured cigarettes, tobacco roll-ups, cigars, or pipe sessions in the past 7 days, and salivary anabasine concentration is <1ng/ml or, in the absence of a salivary anabasine concentration, the level of CO is recorded as <10 ppm.

Abstinence = 0 (no) if the participant has reported any manufactured cigarettes, tobacco roll-ups, cigars, or pipe sessions in the past 7 days, or if the participant has reported no manufactured cigarettes, tobacco roll-ups, cigars, or pipe sessions in the past 7 days and the salivary anabasine concentration is ≥1ng/ml or, in the absence of a salivary anabasine concentration, the level of CO is recorded as ≥10ppm.

4.1.2.2 Smoking Reduction

The achievement of smoking reduction is assessed by means of the participant's self-reported cigarette consumption at the two month follow-up, accompanied by evidence of reduced smoke intake from a CO measurement lower than baseline. This is a derived binary outcome and the variable will be coded as yes/no. N.B. Those who meet criteria for abstinence will be classed as reducers.

Smoking reduction = 1 (yes) if the participant has reported a decrease of ≥50% compared to baseline in the average number of cigarette equivalents (calculated as described in section 3.1.2) in the past 7 days, and CO measurement is lower than the baseline value.

Smoking reduction = 0 (no) if the participant has not reported a decrease of ≥50% compared to baseline in the average number of cigarette equivalents (calculated as described in section 3.1.2) in the past 7 days, or CO measurement is not lower than the baseline value.

4.1.2.3 Primary efficacy analysis

We will present the number and proportion of participants who abstain from smoking in each group, by self-reported smoking status biochemically confirmed either by anabasine concentration or CO value, as specified in section 2.1.1. A mixed effects log-binomial regression model will be applied to the data and will include the

abstinence outcome, time (2 month follow-up and 8 month follow-up), trial arm and a trial arm x time interaction, with GP practice included as a random effect. The treatment effect will be reported as a relative risk (RR) with 95% confidence interval (CI) and 2-sided p-value. A similar procedure will be used to analyse the proportion of participants who reduce smoking. Analyses will be carried out on an intention-to-treat basis, according to the Russell Standard [3], where participants lost-to-follow up are assumed to be smokers or not to have reduced and we will impute missing anabasine concentrations and CO values with the baseline value. Participants who have died or genuinely moved away will be excluded from both the numerator and denominator in the analysis, as specified by the Russell Standard (see section 3.2).

5 SECONDARY ANALYSIS

5.1.1 DEFINITIONS AND DERIVED VARIABLES

5.1.1.1 SMOKING CESSATION

5.1.1.1.1 7-DAY POINT PREVALENCE ABSTINENCE AT 8-MONTHS

The achievement of 7-day point prevalence abstinence is assessed by means of the participant's self-reported smoking status at the eight month follow-up. Self-reported abstinence at eight months is verified by an exhaled CO of <10 ppm. This is a derived binary outcome and the variable will be coded as yes/no.

Abstinence = 1 (yes) if the participant has reported no manufactured cigarettes, tobacco roll-ups, cigars, or pipe sessions in the past 7 days, and the level of CO is recorded as <10 ppm, or anabasine concentration of <1ng/ml if CO measurement unavailable.

Abstinence = 0 (no) if the participant has reported any manufactured cigarettes, tobacco roll-ups, cigars, or pipe sessions in the past 7 days, or if the participant has reported no manufactured cigarettes, tobacco roll-ups, cigars, or pipe sessions in the past 7 days and the CO level ≥10ppm or anabasine concentration is ≥1ng/ml if CO measurement is unavailable.

5.1.1.1.2 6-MONTH PROLONGED ABSTINENCE

The achievement of six-month prolonged abstinence will be determined using the Russell standard criteria:

Abstinence = 1 (yes) if the participant has reported smoking fewer than five cigarette equivalents between two and eight month follow-ups, confirmed by an anabasine concentration of <1ng/ml at two months (or CO<10ppm at two months if an anabasine concentration is unavailable) and an exhaled CO concentration of <10ppm at eight months, (or anabasine concentration of <1ng/ml at eight months if CO measurement unavailable).

Abstinence = 0 (no) if the participant has reported smoking more than five cigarette equivalents between two and eight month follow-ups, or if the participant has reported smoking fewer than five cigarette equivalents between two and eight month follow-ups and the anabasine concentration is ≥1ng/ml or CO level ≥10ppm.

5.1.1.2 SMOKING REDUCTION

Smoking reduction will be assessed several ways:

1. By mean change in CO value from baseline to two months. This will be analysed as a continuous variable. The unit is parts per million (ppm).
2. Percentage reduction in participants' self-reported cigarette equivalents per day in the last 7 days from baseline to two months, using the same rules as described above.
3. Percentage reduction in participants' self-reported cigarette equivalents per day in the last 7 days from baseline to eight months, using the same rules as described above.

5.1.2 SECONDARY EFFICACY OUTCOMES

We will present the number and proportion of participants who abstain from smoking at eight months in each group for 7-day point prevalence abstinence and 6-month prolonged abstinence outcomes. As described above for the primary analysis in section 4.1.2.3, a mixed-effects log-binomial regression model will be applied to the data and the treatment effect will be reported as a relative risk (RR) and 95% confidence interval (CI) and 2-sided p-value, adjusted for GP practice as a random effect.

For smoking reduction outcomes, we will report the mean (SD) change in CO from baseline to two months and cigarettes per day from baseline to two months and eight months for each group. A mixed effects linear regression model will be applied to the data and will include time (two month follow-up and eight month follow-up), trial arm and a trial arm x time interaction, with GP practice included as a random effect. We will report the difference, 95% CI and p-value. We will assess reduction outcomes in this way on the population as a whole and separately in non-abstainers only.

Assumptions of linear regression will be assessed and if violated an appropriate transformation will be investigated. If none is found, a Mann-Whitney test will be adopted and the median (IQR) will be used to summarise the data and difference in medians (95% CI) will be reported.

5.1.3 Analysis of non-efficacy outcomes

1. Recruitment and follow-up of patients

- We will calculate the proportion of people who respond to letters of invitation (by dividing the number of people who respond to letter invitations by the number of participants from the target population who were sent letters).
- We will calculate the proportion who consent to enrolment into the study (by dividing the number of people who consented by the number of people who were eligible to take part).
- We will calculate the proportion of people who complete follow-up at two months (by dividing the number of people completing data collection at follow-up by the number of participants randomised).
- We will calculate the proportion of people who complete follow-up at eight months (by dividing the number of people completing data collection at follow-up by the number of participants randomised).

We will examine these outcomes separately at each recruitment centre to assess the generalisability of our recruitment procedures. Proportions will be reported using descriptive statistics.

2. Patient uptake and use of e-cigarettes

For examining uptake of e-cigarettes, we will:

- Calculate the proportion of participants in the intervention group who take up the offer of an e-cigarette (by dividing the number of people who accepted the e-cigarette by the number who were offered an e-cigarette in the intervention group).

For assessing use of e-cigarettes at two month follow-up in both trial arms, we will:

- Calculate the proportion who continue to use the e-cigarette at two month follow-up. Proportions will be reported using descriptive statistics. Continued use of e-cigarettes is defined as use on >50% days between baseline and follow-up. This will be calculated from the question, 'Are you currently using the e-cigarette' and if the response is yes, the participant must report using the e-cigarette at least weekly or daily from the ECDI (question 1, Table 1) at each follow-up.
- Calculate the mean and standard deviation for length of time using the e-cigarette.
- Summarise descriptively the brand of e-cigarette used in current and past users, reporting on the proportion of people who are using /used the study-specific e-cigarette.
- Summarise descriptively the strength of nicotine e-liquid used in current and past users, as categorical data using proportions.
- Summarise descriptively the type of e-liquid flavours used in current and past users, as categorical data using proportions.

- Calculate the severity of e-cigarette dependence at two months using the Electronic Cigarette Dependence Index (ECDI), as shown in Table 1. The scores from the individual questions are summed together to give a total score. This total will be used for summaries and statistical analyses. A higher score indicates stronger e-cigarette dependency. The change from baseline total score to two-month follow up will be summarised descriptively for each group, with means and standard deviations reported.

For assessing use of e-cigarettes at eight month follow-up in both trial arms, we will:

- Calculate the proportion who continue to use the e-cigarette at eight month follow-up. Proportions will be reported using descriptive statistics. Continued use of e-cigarettes is defined as use on >50% days between baseline and follow-up. This will be calculated from the question, 'Are you currently using the e-cigarette' and if the response is yes, the participant must report using the e-cigarette at least weekly or daily from the ECDI (question 1, Table 1) at each follow-up.
- Calculate the mean and standard deviation for length of time using the e-cigarette.
- Summarise descriptively the brand of e-cigarette used in current and past users, reporting on the proportion of people who are using/used the study-specific e-cigarette.
- Summarise descriptively the strength of nicotine e-liquid used in current and past users.
- Summarise descriptively the type of e-liquid flavours used in current and past users.
- Calculate the severity of e-cigarette dependence at eight months using the ECDI, using the same methods above for the two-month ECDI analysis.

Table 1. Electronic Cigarette Dependence Index (ECDI) questions, responses and scoring

Question	**Response Choices**	**Score**
1. How often do you use the electronic cigarette?	Less than weekly Weekly but not daily 0-4 times per day 5-9 times per day 10-14 times per day 15-19 times per day 20-29 times per day 30+times per day	0 0 0 1 2 3 4 5
2. On days that you can use your electronic cigarette freely, how soon after you wake up do you first use your electronic cigarette?	Within 5 minutes 6 - 15 minutes 16 - 30 minutes 31 - 60 minutes 1-2 hours After 2 hours	5 4 3 2 1 0
3. Do you sometimes awaken at night to use your electronic cigarette?	Yes No	1 0
4. If yes, how many nights per week do you typically awaken to use your electronic cigarette?	0-1 nights 2-3 nights 4+ nights	0 1 2
5. Do you use an electronic cigarette now because it is really hard to quit?	Yes No	1 0

6. Do you ever have strong cravings to use an electronic cigarette?	Yes No	1 0
7. Over the past week, how strong have the urges to use an electronic cigarette been?	None Slight Moderate Strong Very Strong Extremely Strong	0 0 1 1 2 2
8. Is it hard to keep from using an electronic cigarette in places where you are not supposed to?	Yes No	1 0
9. Did you feel more irritable because you couldn't use an electronic cigarette?	Yes No	1 0
10. Did you feel nervous, restless, or anxious because you couldn't use an electronic cigarette?	Yes No	1 0

Total scoring: 0–3= not dependent, 4–8 low dependence, 9–12 medium dependence, 13+ = high dependence.

3. Contamination of randomisation
   For assessing contamination, we will:

- Calculate the proportion of consultations where e-cigarette advice and/or the offer of an e-cigarette was given to control group participants. Criteria for contamination (where contamination =1, no contamination =0) will therefore include cases where the participant is randomised to the control group ("NIL") but given EC advice. Proportions will be reported using descriptive statistics.

4. Nicotine intake and cigarette dependence
   For changes in nicotine intake, we will:

- Calculate the mean change in salivary cotinine concentrations from baseline to two-month follow-up for each group and the difference and 95% CI will be computed using linear regression with adjustment for GP practice and baseline salivary cotinine. The unit is ng/ml. Assumptions of linear regression will be assessed and if violated an appropriate transformation will be investigated. If none is found then the Mann-Whitney test will be adopted and the median (IQR) will be used to summarise the data and difference in medians (95%CI) will be reported.

   For assessing cigarette dependence at two months and eight months, we will:

- Calculate the severity of cigarette dependence using the six-item Fagerstrom Test for Cigarette Dependence (FTCD), as shown in Table 2. The FTCD will be re-administered at two and eight month follow-ups. The scores from the individual questions are summed together to give a total score between 0 and 10 for each visit. This total will be used for summaries and statistical analyses. A higher score indicates stronger dependency. The change from baseline total score will be summarised for each follow-up visit for each group, with means and standard deviations reported. A mixed effects linear regression model will be applied to the data and will include time (two month follow-up and eight month follow-up), trial arm and a trial arm x time interaction, with GP practice included as a random effect. We will report the difference, 95% CI and p-value.

Table 2 Fagerstrom Test for Cigarette Dependence questions, responses and scoring

Question	**Response Choices**	**Score**
1. How soon after you wake up do you smoke your first cigarette?	Within 5 minutes 6-30 minutes 31-60 minutes After 60 minutes	3 2 1 0
2. Do you find it difficult to refrain from smoking in places where it is forbidden e.g. at church/mosque/temple, at the library, in the cinema, etc?	Yes No	1 0
3. Which cigarette would you hate to give up the most?	The first one in the morning Any other	1 0
4. How many cigarettes/day do you smoke?	10 or less 11-20 21-30 31 or more	0 1 2 3
5. Do you smoke more frequently during the first hours after waking than during the rest of the day	Yes No	1 0
6. Do you smoke if you are so ill that you are in bed most of the day?	Yes No	1 0

* Score: 1-2 = low dependence ; 3-4= low to moderate dependence; 5-7=moderate dependence; 8+= high dependence

5. Fidelity

- Eligibility
  We will compare responses recorded by the practitioner on the patient ineligibility card on whether the practitioner randomised the patient and reasons for not doing so with the audio recording of the consultation. The reasons for not randomising the patients include the following: Patient no longer smokes; patient accepted usual care smoking advice and treatment; patient asked about e-cigarettes or is currently using them; it would have been clinically inappropriate to do so; it was not appropriate during the consultation at this time; or an alternative special reason. A correction will be made if the audio recording reveals an alternative reason to what was recorded on the patient ineligibility card. The number and proportion of correct eligibility decisions will be presented using descriptive statistics.

- Delivery of usual care
  Due to the volume of audio-recordings of consultations, we will select at random a third of all recordings (approximately 100) and purposively sample from each GP practice within each research centre. Within each GP practice we will select patients from each trial arm by practitioner.

Using descriptive statistics, we will report the proportion of consultations where the practitioner:

- Asked the participant about their smoking status, with the total number of participants randomised as the denominator.
- Gave brief smoking management and cessation advice, with the total number of participants randomised as the denominator.
- Offered a referral to the stop smoking services or offered smoking cessation treatment, with the total number of participants randomised as the denominator.

- Delivery of intervention (in intervention group only)

  As there are two sources of data on the delivery of the intervention (practitioners' self-reported data and data derived from audio-recordings of the consultations) we will present all self-reported data and randomly select 100 recordings to check for accuracy, using the sampling method described above in the analysis for usual care. A correction will be made if the audio recording reveals that the response given was incorrect.

  Using descriptive statistics, we will report the proportion of consultations where the practitioner:

  - Advised their patient about e-cigarettes, with the number randomised to the intervention group as the denominator.
  - Offered the patient an e-cigarette starter pack, with the number randomised to the intervention group as the denominator.
  - Recorded that the patient accepted the e-cigarette starter pack, with the number offered an e-cigarette as the denominator.

6. Practitioners' knowledge and attitudes towards offering e-cigarettes
   For practitioners' knowledge and attitudes to offering e-cigarettes to smokers, change in frequency in each response from pre-trial to post-trial will be calculated for each question and presented in a bar chart.

- Total score for self-efficacy will be calculated by summing the four questions on self-efficacy and the pre and post total scores will be compared using a paired t-test.
- Total score for outcome expectancies will be calculated in the same way, by summing the two items on outcome expectancies and comparing pre and post total scores using a paired t-test.

  If assumptions of normality are not met, a Wilcoxon signed rank test will be performed on the difference between the scores.

7. Patient acceptability of the intervention
   Participants' reactions to the practitioner discussing smoking will be reported using descriptive statistics including the number of observations and their frequencies in each category. The two questions, how helpful and appropriate they found the practitioners' advice, will be analysed separately, using an ordinal mixed effects regression analysis, which includes a fixed effect for intervention and a random effect for GP practice. Prior to analysis, a cross tabulation of the data (randomisation group X reaction category) will be considered. If there are cells with zero or small counts, adjacent categories will be combined. In addition to the analysis of these scores, we will summarise, for presentation purposes, the proportions of people who selected each of the five different scores for each question, or combine where appropriate and compare between interventions using a chi-squared test.

   For patient attitudes towards e-cigarettes, cutting down and stopping smoking, change in frequency in each response from baseline to two month follow up will be calculated for each question and presented in a bar chart.

- Total score for self-efficacy will be calculated by summing the four questions on self-efficacy and the baseline and two month total scores will be compared using a paired t-test.
- Total score for outcome expectancies will be calculated in the same way, by summing the two items on outcome expectancies and comparing baseline and two month scores using a paired t-test.

If assumptions of normality are not met, a Wilcoxon signed rank test will be performed on the difference between the scores.

The helpfulness of resources used by participants in the intervention arm will be reported using descriptive statistics, as above, including the number of observations and their frequencies in each category for the following:

- Number contacted by an experienced vaper, expressed as a proportion with the total number of responders as the denominator.
- Helpfulness of initial advice offered by e-cigarette user, with frequencies (%) for each category reported
- Number that made contact with the vape team, expressed as a proportion with the total number of responders as the denominator.
- Helpfulness of advice offered by e-cigarette user, with frequencies (%) for each category reported.
- Number of participants that read the practical support booklet, expressed as a proportion with the total number of responders as the denominator.
- Helpfulness of practical support booklet, with frequencies (%) for each category reported.
- Number of participants that accessed the study website, expressed as a proportion with the total number of responders as the denominator.
- Helpfulness of study website, with frequencies (%) for each category reported.

6 MODEL ASSUMPTIONS, OUTLIERS AND MISSING DATA

6.1 HANDLING MISSING DATA

Primary analysis will be by ITT with missing outcomes filled by BOCF. The patterns of availability of outcome data for all primary and secondary outcomes will be summarised for both trial arms.

Randomised participants who withdraw from the study for any reason will not be included in regression models for smoking reduction and cessation.

6.2 HANDLING OUTLIERS

A possible outlier is defined as a data-point three standard deviations from the mean of its distribution. For outliers that have not already been queried in data cleaning, they will be queried for double-checking at this stage and updated as appropriate. Analysis will proceed by retaining plausible outliers. Values which are not considered plausible will be set to missing.

6.3 MULTIPLE COMPARISONS AND MULTIPLICITY

In order to correct the type 1 error rate for the fact that there are two primary outcomes we will be using the Holm-Bonferroni method of adjustment [1]. The smaller *P* value will be compared to an alpha of 0.025 (this will probably be for reduction in smoking) and if this is significant, the larger *P* value (which will probably be for cessation) will be compared to an alpha of 0.05.

6.4 MODEL ASSUMPTIONS

Assumptions of normality and constant variance in linear regression models will be assessed using residual and other diagnostic plots, and if violated, an appropriate transformation will be investigated. If none is found then

a Mann-Whitney test will be adopted and the median (IQR) will be used to summarise the data and difference in medians (95% CI) will be reported.

7 SENSITIVITY ANALYSIS

Baseline Observation Carried Forward (BOCF) will be used in the ITT analysis. This a procedure which assumes that data are missing not at random and is considered as the worst case imputation (i.e. assigning the worst possible value of the outcome to dropouts for intervention failure).

For primary outcomes only, baseline variables found to be predictive of missingness (using logistic regression) will be included in the model together, as a sensitivity test. We will also repeat the analyses using only those with data at follow-up.

For the analysis of smoking reduction, we will repeat the analyses in sections 4.1.2.3 and 5.1.2 using only the participant's self-reported cigarette consumption at two months and eight months, where the following will apply:

Smoking reduction = 1 (yes) if the participant has reported a decrease of ≥50% compared to baseline in the average number of cigarette equivalents (calculated as described in section 3.1.2) in the past 7 days.

Smoking reduction = 0 (no) if the participant has not reported a decrease of ≥50% compared to baseline in the average number of cigarette equivalents (calculated as described in section 3.1.2) in the past 7 days.

8 SUBGROUP ANALYSES

There are no hypothesised subgroup effects, so all subgroup analyses will be exploratory. We will examine effects split by:

1. Degree of tobacco dependence measured at baseline using the FTCD as a categorical variable, with low vs high dependency categories (1-4 = low dependency, 5+= high dependency). It is possible that this approach may be particularly helpful for those with higher dependence, who find abrupt quitting too difficult.
2. Socioeconomic status, measured by Index of Multiple Deprivation score. We have no hypothesis that the effect may vary, but examining the equity impact of any intervention is important.
3. Whether participants have a mental health disorder or not, because there is a widespread assumption that cutting down is particularly suitable for people with mental health disorders. Here, we define a mental health disorder as anyone reporting depression or schizophrenia, bipolar disorder or other psychoses.

The subgroup analyses will be done on the same population as used in the primary analyses of the two primary outcomes using the same regression equation but adding an interaction term between the subgroup of interest and group allocation.

9 ADDITIONAL EXPLORATORY ANALYSIS

No exploratory analyses are planned at this stage.

10 SAFETY ANALYSIS

10.1 ADVERSE EVENTS

For the purposes of the trial, we will record adverse events in the case report form by asking the participant to complete a symptoms checklist at the two-month follow-up appointment. The checklist will contain symptoms

commonly reported in previous studies on e-cigarettes, including throat/mouth irritation, cough, dry mouth, shortness of breath, headache, nausea, dizziness, stomach pain and palpitations. Participants will rate whether they have been troubled by any of these symptoms in the past 24 hours, on a five-point Likert scale from "Not at all" to "Extremely". The number (%) of participants having each symptom and its severity will be presented, with the denominator being persons reporting on the presence of that symptom with no imputation of missing data.

There are no expected serious related adverse events in this study. However, to provide further evidence on this, we will collect data on the occurrences of serious adverse events at each follow-up. Serious adverse events were defined as resulting in admission to hospital, death or life threatening events, permanent disability, or congenital abnormality. This excluded planned admissions to hospital. SAEs will be assessed in a blinded manner for relatedness to the intervention. We will report the number of events and whether any were judged as possibly, probably or definitely related to EC use. We will compare trial arms using a chi squared test or fisher's exact test if the numbers in any cell of the 2 x 2 table are <5.

11 VALIDATION

The primary and safety analyses will be validated by a senior trial statistician (or delegate). The analysis report will also be reviewed in its entirety.

12 CHANGES TO THE PROTOCOL OR PREVIOUS VERSIONS OF SAP

The following changes are pre-specified and have been implemented before data lock:

Subsequent to writing the protocol and receiving advice from the chair of our Trial Steering Committee, we became concerned about the use of anabasine as a marker for determining smoking reduction [4]. We had anticipated verifying reduced smoke intake with a salivary anabasine concentration lower than baseline. However, we have been advised from the laboratory – who are responsible for the assay and analysis of the saliva samples – that anabasine cannot be used as a marker for smoking reduction. We have therefore specified that self-reported smoking reduction will be verified by CO only.

The following secondary analyses (in section 5.1.1.2) are not described in the protocol but are pre-specified here:

- Mean change in CO values from baseline to two months.
- Percentage reduction in self-reported cigarettes per day from baseline to two months.

We previously stated in the protocol that *nicotine* dependence would be measured using the Fagerstrom Test for Cigarette Dependence. We have defined this as *cigarette* dependence in the current version of the SAP.

13 REFERENCES

1. Holm S: **A Simple Sequentially Rejective Multiple Test Procedure**. *Scandinavian Journal of Statistics* 1979, **6**(2):65-70.
2. Moore D, Aveyard P, Connock M, Wang D, Fry-Smith A, Barton P: **Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis**, vol. 338; 2009.
3. West R, Hajek P, Stead L, Stapleton J: **Outcome criteria in smoking cessation trials: proposal for a common standard**. *Addiction* 2005, **100**(3):299-303.
4. Feldhammer M, Ritchie JC: **Anabasine Is a Poor Marker for Determining Smoking Status of Transplant Patients**. *Clinical Chemistry* 2017, **63**(2):604-606.

14 APPENDICES

Appendix I. Schedule of procedures

	Visits			
	Baseline	**Day 0 Annual review (Intervention)**	**Two-month follow-up**	**Eight-month follow-up**
Procedures				
Eligibility assessment	x	x		
Informed consent	x			
Randomisation & Allocation		x		
Demographics	x			
Medical history	x			
Current medications	x		x	x
Smoking history, nicotine dependence (FTCD), motivation to stop questionnaires	x			
CO measure*	x		x	x
Saliva sample*	x		x	x
Laboratory tests for anabasine & cotinine	x		x	x
Randomisation and intervention delivery		x		
Behaviour checklist (practitioner adherence)		x		
Adverse event assessments			x	x
Self-reported smoking behaviour*, product use and adherence questionnaire	x		x	x
Patient self-efficacy and outcome expectancies questionnaire	x		x	
Post-consultation patient reaction questionnaire		x		
Patient, practitioner and vape team interviews			x	
Recording withdrawal			x	x
Recording loss to follow up			x	x

*Primary outcome measures

Appendix II. Flow diagram of trial participants