Statistical Analysis Plan

A randomised controlled trial to examine the efficacy of e-cigarettes compared with nicotine replacement therapy, when used within the UK stop smoking service

Version: 1.0
Date: 08.01.2018

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Introduction

Purpose of statistical analysis plan

The purpose of this document is to provide details of the statistical analyses and presentation of results to be reported within the principal paper(s) of the TEC trial. Subsequent papers of a more exploratory nature (including those involving baseline data only) will not be bound by this strategy but will be expected to follow the broad principles laid down in it. Any exploratory, post hoc or unplanned analyses will be clearly identified in the respective study analysis report.

The structure and content of this document provides sufficient detail to meet the requirements identified by the International Conference on Harmonisation (ICH) and the Barts CTU SOPs.

Members of the writing committee

Hayden McRobbie, Anna Phillips-Waller, Peter Hajek and Irene Kaimi were primarily responsible for writing the Statistical Analysis Plan, with input from other members of the Trial Management Group.

The document has been finalised by blinded members of the Trial Management Group and a blinded statistician.

Summary

Background: Electronic cigarettes (EC) have a potential to increase the reach and reduce the costs of the UK Specialist Stop Smoking Service (SSS). Data are needed on their efficacy compared to standard stop smoking medicines, such as nicotine replacement treatment (NRT), which is the most commonly used smoking cessation medicine in the UK.
Design: Randomised controlled trial.
Setting: Four SSS that provide evidence-based treatment to smokers who are typically highly dependent.
Strategy for research and modelling: A straightforward trial comparing EC to no treatment is not ethically acceptable and it will also not clarify the value of EC in the current treatment landscape. Hence, smokers will be randomised to either the usual care arm (UC) that comprises of standard specialist stop-smoking treatment, i.e. behavioural support consisting of 6 weekly support sessions combined with NRT; or to the EC arm that comprises the same behavioural support combined with EC.
Sample: 886 smokers seeking help who are 18 years or older and are not pregnant.

Health technologies being assessed: EC are battery-powered devices that deliver a vaporised liquid nicotine solution in propylene glycol or glycerol. No tobacco, smoke or combustion is involved in their operation and no clinically significant levels of any harmful chemicals have been detected in EC vapour. We provide a starter-kit to participants in the EC arm. We have consulted EC users who advise that the flavour and strength of the refill e-liquid is an important but very personal choice. We will therefore direct participants to select and purchase their own refill e-liquid. This will (a) ensure that people use a refill e-liquid they like; (b) reflect what happens in 'real life'; and (c) avoid giving the EC arm an advantage of free treatment when some participants in the UC arm will have to pay a prescription charge.

Recruitment: Smokers seeking help will be recruited from local SSS and by advertisements in local papers, posters/leaflets and via social media.

Procedure: Prospective participants will attend a screening session and those eligible will provide informed consent, demographic data and details of smoking history, and be randomised on their quit date to one of the two study arms.

Usual Care (UC) arm*:* Participants will be assisted in selecting NRT of their choice as per usual practice. The NRT will be provided as per standard practice. Participants will attend 6 weekly support sessions and will be contacted by telephone for follow up at 6 and 12 months post quit. Participants reporting abstinence or 50% or more reduction in cigarettes per day at 12 months will be invited for CO validation.

EC arm*:* Participants will be given an EC starter-kit (18mg/ml nicotine). They will be provided with instructions on how to operate the EC. An information sheet written in collaboration with experienced EC users will also be provided. Participants will be advised on how to obtain further supplies themselves. Support and follow-up contacts will be identical to those in the UC arm.

Measurement of outcomes and costs: The primary outcome measure will be sustained abstinence from 2 weeks post-TQD to one year defined as per Russell validated by CO reading<8 ppm at Week 4 and at one year. Secondary outcomes will include sustained abstinence from 6 months to one year, abstinence at 4-weeks and 6 months, smoking reduction in participants who did not achieve full abstinence, ratings of the treatment, adverse events, and the cost-efficacy of the interventions. An intention to treat analysis will be used with participants lost to follow-up included as non-abstainers.

Sample size: Based on figures from the UK usual care treatment, the 12-month validated abstinence rate associated with UC was initially expected to be 14%. We wished to detect a RR of 1.7 (EC rate = 24%) with 0.95 power, but also have reasonable power (say, 0.75) if the RR should be as low as 1.5 (EC rate = 21%). This latter figure would still represent a clinically significant difference. To achieve these levels of power (2-sided, alpha = 0.05, continuity correction), a total of 886 participants (443 in each group) are required. New national outcome statistics published in 2016, however, show the UC quit rate dropping to 8%. This comprised general practice a pharmacy

services with quit rates of 5% and specialist support with quit rates of 10% for individual and 12% for group support. Using a quit rate of 10% in the UC arm that provides multi-contact support, and 17% in the EC arm (RR=1.70) the study sample size still provides 86% power to detect such a difference with a two-tail test of proportions.

Background

EC are battery-powered devices that provide inhaled doses of nicotine by delivering a vaporised liquid nicotine solution in propylene glycol or glycerol. No tobacco, smoke, or combustion is actually involved in their operation.

EC have largely been marketed as a 'lifestyle' product for smokers who want to reduce the risks of smoking. EC provide levels of nicotine similar to those provided by NRT, but they might have an advantage over existing NRT products because of their ability to provide more realistic sensorimotor and behavioural replacement for smoking.

Current smoking cessation treatments generally provide a combination of behavioural support and evidence-based medicines to target withdrawal discomfort, but sensorimotor factors are not well addressed. EC provide sensations similar to smoking a cigarette by emitting a smoke-like mist or vapour, and provide taste and throat sensations which are closer to smoking than those provided by oral NRT e.g. the nicotine inhalator. There is some evidence that these factors are important for smokers and that their inclusion enhances treatment efficacy [1].

Effects of EC on smoking

At the time of writing there are three published randomised controlled trials examining the effects of EC in helping people stop smoking. One examined their use in people who wanted to quit [2], and two in those who did not [3, 4]

The first trial, which examined the use of EC in people who wanted to quit, compared nicotine-containing electronic cigarettes with 21mg nicotine patches and with non-nicotine electronic cigarettes. At 6-month follow-up there were no significant differences in validated continuous abstinence (7.3% nicotine EC, 5.8% nicotine patch, and 4.1% non-nicotine EC) [2].

The second study examined the effect of EC use (two different doses for 12 weeks) compared to non-nicotine EC in 300 smokers not intending to quit. At one-year follow-up there were no statistically significant differences in 6-month, biochemically verified, abstinence rates (13%, 9%

and 4% in the three groups respectively [3]. Both of these trials used cig-a-like devices that had poor nicotine delivery and are no longer available on the market.

The third RCT examined the use of tank system EC, compared with no intervention in 48 smokers who did not want to quit. At 8-week follow-up, 34% of those given an EC to use had quit smoking compared to none in control group [4].

The first published systematic review, which has recently been updated, showed that EC with nicotine help smokers quit for at least 6 months compared with no nicotine e-cigarettes (RR= 2.29, 95% CI: 1.05-4.96; 9% vs. 4%) [5]. The review gives these findings a 'low' confidence rating using GRADE standards, not because of poor quality studies, but because the systematic review included only two studies.

There is good rationale for why EC could help people stop in that they can deliver nicotine and alleviate urges to smoke. However, more, well-designed, clinical trials are needed to confirm this.

Changes from planned analysis in the protocol

None.

Changes from SAP version 1.0

Not applicable.

Study objectives and endpoints

Study objectives

Primary Objective

To determine the 12-month sustained, biochemically validated abstinence rates in smokers using EC compared to smokers using standard NRT.

Secondary Objectives

1. Abstinence rates between 6 and 12 months.
2. Abstinence rates at 4 weeks and 6 months.
3. Effects of the two treatments on smoking reduction in participants who did not achieve full abstinence.
4. Changes in urges to smoke and other tobacco withdrawal symptoms at 1 and 4 weeks.
5. Ratings of the two treatment approaches by patients.
6. Rates of adverse reactions associated with the use of EC compared to standard NRT.
7. Cost-effectiveness of EC compared to standard NRT.

Outcome measures

Primary outcome measure

The primary outcome measure is carbon monoxide (CO) validated sustained abstinence rates at 52 weeks post target quit date (TQD), defined as per Russell Standard [6].

Secondary outcome measures

The secondary outcome measures are:

1. CO validated sustained abstinence rates between 24 and 52 weeks
2. Sustained abstinence rates at 4 and 24 weeks post TQD (CO validated at 4 weeks)
3. 7-day point prevalence abstinence at 4, 24 and 52 weeks
4. Smoking reduction in participants who did not achieve full abstinence
5. Changes in urges to smoke and other tobacco withdrawal symptoms at 1 and 4 weeks
6. Treatment ratings (e.g. satisfaction, helpfulness)
7. Adverse reactions
8. Cost-efficacy of the interventions.

Abstinence at 4 weeks post TQD is defined as a self-report of no smoking of conventional cigarettes (not a puff) for the previous 2 weeks, validated by a CO reading of <8ppm. Participants who do not provide a CO reading at Week 4 will be considered to be smoking at 4 weeks. 24 and 52 week sustained abstinence will be calculated in accordance with the Russell Standard [6] as a self-report of smoking no more than 5 cigarettes since 2 weeks post TQD, validated by CO readings of <8ppm at the 52 week follow up. Participants lost to follow up or not providing biochemical validation will be included as non-abstainers.

Study methods

Overall study design and plan

Target for randomisation:	886
Date of first randomisation:	11.05.2015
Date of last randomisation:	01.02.2017
Trial design:	Individually randomised, parallel group
Who is blinded:	Participants and researchers are blinded up until the point of randomization.
Randomised Interventions:	Intervention (EC) vs. control (NRT)
Allocation ratio:	1:1

Study population

The study population consisted of people responding to advertising (typically posters, leaflets, digital media, local papers, on local transport, through GP practises, mail outs to previous attenders, and in local radio/newspaper interviews).

Participants were eligible to take part if they were age 18 years and older, a current smoker accessing a stop smoking service (SSS) and able to read/write/understand English.

Participants were excluded from participating if they were pregnant or breastfeeding, had a strong preference to use or not to use NRT or EC in their quit attempt, were enrolled in other interventional research, or currently using NRT or EC.

Method of treatment assignment and randomisation

Randomisation (1:1 in permuted blocks) was undertaken using a web-based application, set up by the Barts Clinical Trials Unit (Barts CTU), and was stratified by study site. Participants who were eligible and consent to take part were randomly allocated to the experimental or control interventions at the target quit day (TQD) session. The TQD was used as the point of randomisation to limit any differential drop-out. The staff randomising the patient accessed the web-based application when the participant was with them, entering their participant ID number, date of birth and initials into the program. There were no stratification factors within study sites. The allocation was immediately provided by the program.

Treatment masking (Blinding)

Participants could not be blinded to the intervention they were receiving and study staff could not be blinded when providing the interventions. However, collective unblinded data were only seen and analysed for the purposes of the DMECs by the trial statistician. The trial statistician was not involved in the decisions about the analysis and the treatment of deviations after randomisation (e.g. protocol violations, losses to follow up, withdrawals from the study).

All other trial staff who have access to outcome data remained blinded until data analysis was complete. Final data analysis will be conducted blind to treatment allocation.

Sample size determination

The 12-month validated abstinence rate (Primary outcome) associated with UC in our setting was initially assumed to be 14% [7]. Our projection of a feasible rate with the EC is based on our work and two published studies. Our work [8] suggests that EC delivers nicotine quickly, with Tmax occurring within 5 minutes. This is similar to nicotine nasal spray. In a comparative study of the nasal spray + patch versus patch alone in Iceland, 1-year abstinence rates were 27% vs. 11%, Risk Ratio (RR) = 2.45 [9]. More relevant, in a recent cohort study in Italy, a second generation EC achieved 36% CO validated abstinence at 6-months [10]. Assuming 25% relapse between 6 and 12 months [11], this would translate to a 1-year rate of 27%. Relative to our assumed UC rate, this would give RR = 1.9. However, quit rates in countries with little tradition of stop-smoking treatments tend to be much higher than in the UK.

We wish to detect a RR of 1.7 (EC rate = 24%) with 0.95 power, but also have reasonable power (say, 0.75) if the RR should be as low as 1.5 (EC rate = 21%). This latter figure would still represent a clinically significant difference. To achieve these levels of power (2-sided, alpha = 0.05, continuity correction), a total of 886 participants (443 in each group) are required.

Notes: Since the study protocol was written, a new evaluation of the UK stop smoking services was published [12]. The validated one-year quit rate has declined to 8%. This comprised general practice and pharmacy services with quit rates of 5% and specialist support with quit rates of 10% for individual and 12% for group support. The decline is probably due to a 'hardening' of treatment population, e.g. the services see an increasing number of re-attenders, people with serious health issues etc. Using a quit rate of 10% in the UC arm that provides multi-contact support, and 17% in the EC arm (RR=1.70) the study sample size still provides 86% power to detect such a difference with a two-tail test of proportions.

Assuming the true percentage in both arms is 10%, the 95% confidence interval for the difference in proportions will have width of +/-4% around the observed difference.

If the difference in proportions is non-significant, we will undertake a non-inferiority analysis, using a two-sided confidence interval of the difference in the abstinence percentages between the two arms. Assuming that the true percentages are 10% in the control arm and 12% in the intervention arm, our sample size of 886 will provide 88% power to exclude a difference in favour of the standard group of 4% or more.

Data collection

Baseline

The following variables were collected at baseline:

- ***Demographics:*** includes age, sex, marital status, ethnicity, employment, level of education, eligibility for free prescriptions,
- ***Smoking measures:*** Fagerstrom Test for Cigarette Dependence (FTCD) [13], previous stop smoking product use, age first started smoking and whether partner/spouse smokes. Mood and Physical Symptoms Scale (MPSS) [14], carbon monoxide reading
- ***Current Health and Medications***
- ***Health problems checklist***

The following validated questionnaires are also administered at baseline:

- EQ-5D
- Smoking Cessation and Health Service Use Questionnaire

Follow up

The following variables were collected during follow-up visits:

- Current smoking behaviour
- Mood and Physical Symptoms Scale (MPSS) – 1 and 4 weeks post quit only
- Carbon monoxide reading
- Allocated product use, helpfulness, taste and satisfaction ratings (1 and 4 weeks post quit only), purchase and reasons for stopping (where applicable)
- Non-allocated product use and purchase
- Current health and medications
- Health problems checklist

The following validated questionnaires are also administered at 6 and 12 month follow up:

- EQ-5D
- Smoking Cessation and Health Service Use Questionnaire

Timing of data collection

The recruitment period was: 11 May 2015 – 01 February 2017 (22 months) and the study sessions were conducted as follows:

Week -1	Baseline
Week 0:	Randomisation (TQD)
Weeks 1-4:	Treatment sessions, 1, 2, 3 and 4 weeks post TQD (Q+1, Q+2, Q+3 and Q+4)
Month 6:	Follow-up, 24 weeks post TQD (Q+24)
Month 12:	Follow-up, 52 weeks post TQD (Q+52)

Database

Description

Data were entered into the online database, 'Oracle Database 11g', hosted at the Barts Cancer Centre. The Electronic Data Capture forms are web based and built using Java with data validation in JavaScript (Java framework Struts 2).

Data quality

The study team check the data for discrepancies each week, and clarify any potential data entry errors with the relevant advisor/researcher or participant. When recruitment and follow-up are complete, the study team will clean the data in the following way: values for each variable will be sorted, and those at the extremes will be checked to ensure that they are within the expected range.

Source data verification will also be conducted where paper CRFs have been used: a random sample of 10% of CRFs will be selected, and the study team will compare all written entries with those entered onto the main study database. The pre-specified data quality target is ≤ 2% discrepancy rate between entries in the CRF and the electronic database. If an error is found in >2% of entries, the quality target for data entry will not have been met, and all CRF data will be cross-checked against data in the study database.

Derived and computed variables

All derived and computed variables will be documented in the analysis programmes.

General issues for statistical analysis

General analysis principles

The main analysis for each outcome will use intention-to-treat (ITT) principles, meaning that all participants with a recorded outcome will be included in the analysis, and will be analysed according to the treatment group to which they were randomised. More information on which participants will be included in each analysis is available in the section below. All p-values will be two sided, and the significance level is set at 5%.

Analyses for all outcomes will be presented as:

- The number of participants included in the analysis, by treatment group. NB. for the primary outcome data this will be all randomised participants – see missing data section below);
- A summary measure of the outcome, by treatment group (e.g. mean (SD) for continuous outcomes, number (%) for binary outcomes);
- A treatment effect (risk ratio of abstinence for EC relative to NRT), with a 95% confidence interval;
- A two-sided p-value.

Missing data for outcomes

To deal with incomplete data (i.e. when patients have missing data at one of the follow-up time points) we will:

- Attempt to follow up all randomised patients even if they discontinue participation.
- Include participants lost to follow-up (missing cases) or not providing biochemical validation as non-abstainers.
- Carry out a sensitivity analysis using different assumptions about missing cases (e.g. using the Hedeker method [15] and last known quit status), as well as analyses excluding cases with missing outcomes. NB. Where a participant misses 52 week follow up, but it is already known from their 3, 4 and/or 24 week follow up that they have smoked more than 5 cigarettes since 2 weeks post TQD, they will be counted as smokers for the primary outcome in sensitivity analyses.

Withdrawn participants

Withdrawn participants (i.e. no further follow up permitted) will be included in the analysis as per intention to treat (counted as smokers for the time points after withdrawal, as per Russell Standard).

Participants who died will be excluded from the sample as per the Russell Standard.

Participants who have moved to an untraceable address (documented by returned letters) and whose telephone numbers and email address are no longer in use will be excluded from the sample from the point that notification was received that they were no longer living at the address and their telephone numbers/email address are no longer in use, as per the Russell Standard. They will be included in the sample analysis up until this point.

Analysis of primary outcome

For the primary analysis the proportion of people remaining abstinent at a year will be compared between the study arms using Chi-squared test. The treatment effect will be the risk ratio of abstinence rates for EC relative to NRT. A secondary binomial regression with log link will also be employed, which will allow for a comparison of the two study arms after adjusting for baseline variables identified as significant using a stepwise selection procedure. The analysis will be stratified by the randomization stratification factor, site; this will be done by adjusting the model using a dummy variable for site.

Sensitivity analyses for primary outcome:

A sensitivity analysis will be conducted with only participants who attended at least one treatment session, i.e. who engaged in treatment, included.

Forty two participants received a different EC device due to discontinuation of the original supply. A sensitivity analysis will be conducted with only these participants included.

To deal with participants who switched study products or used the unassigned study product for at least five consecutive days we will include them in the primary analysis in the groups to which they were randomized, but will also conduct a sensitivity analysis where they will be excluded.

Analysis of secondary outcomes

Smoking cessation and reduction outcomes

For the secondary analyses, we will examine the differences between study arms in the proportions of participants with sustained abstinence from 6 to 12 months, and at 4, 24 and 52 week follow-up,

and sustaining a 50% or greater reduction in baseline cigarette consumption and CO levels at 52 weeks, using Chi-squared test/binomial regression.

Sensitivity analyses for secondary outcomes:

Forty two participants received a different EC device due to discontinuation of the original supply. A sensitivity analysis will be conducted with only these participants included.

We will also examine time to relapse in a secondary analysis using a Cox analysis.

Definitions of smoking cessation and reduction outcomes

Primary outcome:

52 week sustained abstinence will be calculated in accordance with the Russell Standard as a self-report of smoking no more than 5 cigarettes since 2 weeks post TQD, validated by a CO reading of <8ppm at the 52 week follow up.

The following rules will apply to the primary outcome:

- Where a participant misses any (or all) of the previous sessions/follow ups, but self-reports smoking no more than 5 cigarettes since 2 weeks post TQD at 52 week follow up, they will be classed as meeting the primary outcome definition providing their self-report is validated by a CO reading of <8ppm at the 52 week follow up.
- Where a participant reports smoking 1-5 cigarettes at more than one session/follow up but reports smoking no more than 5 cigarettes in total since 2 weeks post TQD at 52 week follow up, they will be assumed to have smoked no more than 5 cigarettes in total since 2 weeks post TQD and will meet the primary outcome definition providing their self-report is validated by a CO reading of <8ppm at the 52 week follow-up.
- Where a participant self-reports abstinence at 4 weeks post TQD, but does not give a CO reading at this time point, and at 52 week follow up self-reports smoking no more than 5 cigarettes since 2 weeks post TQD, they will be classed as meeting the primary outcome definition providing their self-report is validated by a CO reading of <8ppm at the 52 week follow-up.

- Where a participant self-reports abstinence at 4 weeks post TQD but fails CO validation at this time point (i.e. they have a CO reading of greater than 8 at 4 weeks post TQD), they will not be included as a CO validated sustained abstainer at 52 week follow up.
- Where a participant reports being 'currently quit' at 52 week follow up, but has not been contactable to provide any other information, they will **not** be counted as a 52 week sustained abstainer, since they will not have been contactable to arrange a CO validation.
- Where a participant reports being 'currently quit' at 4 and/or 24 weeks post TQD and has not been contactable to provide further information at these time points, but then reports smoking no more than 5 cigarettes in total since 2 weeks post TQD at 52 week follow up, they will be assumed to have smoked no more than 5 cigarettes in total since 2 weeks post TQD and will meet the primary outcome definition providing their self-report is validated by a CO reading of <8ppm at the 52 week follow-up.

Secondary outcomes:

1. CO validated sustained abstinence between 24 and 52 weeks post TQD	No more than 5 cigarettes smoked between weeks 24 and 52 accompanied by a CO reading of < 8ppm at week 52. Where a participant reports being 'currently quit' at 52 weeks post TQD, but has not been contactable to provide any other information, they will **not** be counted as a 24-52 week sustained abstainer, since they will not have been contactable to arrange a CO validation.
2. CO validated sustained abstinence at 4-weeks post TQD	Not a single puff of a cigarette in the last 2 weeks at 4 week follow up accompanied by a CO reading of < 8ppm at 4 weeks post TQD. Where a participant misses Q+3 but reports not a single puff since their last visit at 4 weeks post TQD, accompanied by a CO reading of < 8ppm at 4 weeks post TQD, they will be counted as a CO validated abstainer at 4 weeks post TQD. Where a participant reports being 'currently quit' at 4 weeks post TQD, but has not been contactable to provide any other information, they will **not** be counted as a 4 week abstainer since they will not have been contactable to arrange a CO validation.
3. Sustained abstinence at 24 weeks post TQD	No more than 5 cigarettes smoked since 2 weeks post TQD to 24 weeks post TQD.

		Where a participant misses any (or all) of the previous sessions/follow ups, but self-reports smoking no more than 5 cigarettes since their last visit at 24 weeks post TQD, they will be counted as a 24 week sustained abstainer Where a participant reports smoking 1-5 cigarettes at more than one session/follow up but reports smoking no more than 5 cigarettes in total since their last visit at 24 week follow up, they will be assumed to have smoked less than 5 cigarettes in total since 2 weeks post TQD. Where a participant reports being 'currently quit' at 24 weeks post TQD, but has not been contactable to provide any other information, they **will** be counted as having smoked no more than 5 cigarettes since their last visit, and included as a 24 week sustained abstainer.
4.	7-day point prevalence at 4-weeks post TQD	Not a single puff in the last 7-days
5.	7-day point prevalence at 24-weeks post TQD	Not a single puff in the last 7-days
6.	7-day point prevalence at 52-weeks post TQD	Not a single puff in the last 7-days
7.	Smoking reduction in participants who did not achieve abstinence at 52-weeks	Self-reported daily cigarette consumption at 52 weeks post TQD reduced by at least 50% of baseline consumption accompanied by a CO reading at 52 weeks reduced by at least 50% compared to baseline. NB. Where participants have CO<10 at baseline and report 50% or more cigarette per day reduction at 52 weeks, sensitivity analyses will be carried out including and excluding them. A sub-analysis of self-reported daily cigarette consumption at 52 weeks reduced by at least 50% of baseline consumption without accompanied CO readings will also be conducted. Participants with missing data or who report being 'currently quit' at 52 weeks with no further data provided will be classified as non-reducers.

***See appendix 3 for how data for each outcome was collected**

Differences in tobacco withdrawal symptoms at 1 and 4 weeks.

Between-group differences in urges to smoke, and changes (from baseline) in tobacco withdrawal symptoms will be examined using ANOVA, in both the whole sample, and abstainers only sample.

Treatment ratings (e.g. satisfaction, taste, helpfulness, reasons for stopping product use)

Differences in mean ratings of treatment effects (product helpfulness, taste, satisfaction and reasons for stopping product use) between groups will be examined using ANOVA (or non-parametric tests where normality cannot be assumed) at 1 and 4 weeks post quit with adjustments where needed for normal distribution. NB. Where 2 NRT products were used and rated, the average rating of the two will be taken.

Adverse reactions (ARs)

The frequency of participants reporting each AR (nausea, sleep disturbance or throat/mouth irritation) at least once will be compared between arms using Chi squared test. The MedDRA coding system will be used.

Changes in respiratory problems

Frequency of respiratory problems at baseline and 12 month follow up will be compared between arms using Chi-squared test.

Cost-efficacy of the interventions.

The economic evaluation is conducted alongside the TEC trial by way of a cost-effectiveness analysis. Following NICE guidance, the analysis will be performed from the National Health Service (NHS) and Personal Social Services (PSS) perspective to reflect NHS England decision-making framework [16]. The analysis from a wider perspective will also be conducted to explore the possible societal impact of the intervention. All costs will be presented in 2015/16 Sterling Pounds (£). The objectives of the analysis are:

1. To assess cost-effectiveness of EC over and above UC at 12-month follow-up (primary outcome);
2. To estimate potential long term cost-effectiveness of the intervention.

These objectives will be achieved by combining data collected within the trial and existing models.

Costs estimation

Intervention cost

The intervention consists of six weekly sessions of standard SSS behavioural support for both arms, a starter kit of e-cigarette for the EC arm and supplies of NRT for the UC arm.

The second generation EC used in the trial contains 18mg/ml nicotine e-liquid, the cost of which will be recorded by the research team. The NRT supplies will also be recorded by the research team. The form and dosage of NRT will be matched to all the products with the same chemical name, dosage and form in Prescription Cost Analysis [17] to get the weighted average cost per item of each NRT product. The version of Prescription Cost Analysis will be for the appropriate financial year. Where the information on some aspects is missing (e.g. patches with no dosage recorded), the weighted average cost based on available information will be applied. Due to different approaches of dispensing NRT products between our research sites (direct dispense vs LOR), a conservative assumption is made that once an LOR is provided, the stated NRT products are considered dispensed. This is to avoid underestimating cost to the NHS.

The printing cost of accompanied information and instruction materials for both arms will also be recorded by the research team.

The sessions of behavioural support during the intervention period will be provided by the research team and stop smoking advisors. The attendance will be documented and the average wage rate of a qualified NHS Stop Smoking Service (SSS) advisor will be applied to the number of sessions attended.

Smoking cessation service after the intervention period

Smoking cessation services use after the intervention period, including pharmacotherapies and EC, will be recorded at 6 and 12 months follow up by self-report. The quantities reported will then be multiplied by the unit costs of corresponding services or net ingredient cost of prescribed items.

Health resources use

Participants' use of primary, secondary care and community services will be collected with self-report questionnaire at baseline, 6 and 12 month follow-up for the 6-month period prior to the follow-up. A set of national average costs of the appropriate year will be applied to the quantities reported to estimate the cost of health resources use [18, 19].

Quality of life

The EQ-5D [20] will be completed by patients at baseline, 6 and 12 months with the UK population tariff attributed to estimate utility values [21]. These utility values will then be used to calculate quality-adjusted life years (QALYs) using the area under the curve method [22].

Analysis

Basecase analysis

As the primary outcome will be 12-month sustained, biochemically validated abstinence, a cost-effectiveness analysis will be performed at this time point. The costs will include intervention cost, smoking cessation services cost after intervention period and health resources use cost that has occurred during the 12-month period. The difference in costs between arms will be controlled for health resources use at baseline, age, sex, study site, entitlement of free prescriptions, ethnicity and baseline FTCD. The quality adjusted life years (QALYs) will be calculated during the same time period. The difference in QALYs between arms will be controlled for utility value at baseline, age, sex, study site, entitlement of free prescriptions, ethnicity and baseline FTCD. Combining both, an incremental cost-effectiveness ratio (ICER) of cost per QALY will be calculated to assess the cost-effectiveness of the intervention, comparing with the standard care. The ICER will then be compared with the national willingness-to-pay threshold of £20,000-£30,000 per QALY gained [16].

Uncertainty assessment

The uncertainty around the decision to adopt the intervention will be assessed through a non-parametric bootstrap re-sampling technique. Bootstrapping has been proposed as an efficient approach for calculating the confidence limits for the ICER as its validity does not depend on any specific form of underlying distribution [23-26]. A cost effectiveness acceptability curve (CEAC) will be plotted based on the outcomes of the 5000 bootstrap iterations [27].

A separate sensitivity analysis will be carried out to examine the impact of the assumption of LOR equating dispense on the intervention costs. This will be undertaken by using the actual quantities used reported by the participants as the cost base of the NRT costs. A set of weighted average cost per unit of the NRT products will be extracted from Prescription Cost Analysis [17] with the same approach as in the base case analysis. These unit costs will then be multiplied by the quantities reported of corresponding NRT products.

Given that the current practice for smoking cessation does not provide prescription of EC while allows prescription of pharmacotherapies, a separate analysis will be carried out, including participants' out-of-pocket money for EC and pharmacotherapies, to examine the possible cost-shift from NHS to smokers.

Handling missing data

For the smoking cessation services use after intervention and health resources use, it will only be deemed as missing when all sections under one question are left blank. For instance, where one question has five sub-questions (annotated as a), b), c), etc.), all five will be deemed as missing when all five are left blank. If one of them is answered, the others will be assumed as 0. For EQ-5D-5L, due to the structure of the questionnaire, the whole section is considered missing if any of the five questions is not answered. The missing data in services use and EQ-5D-5L will be imputed using Rubin's multiple imputation method [28].

To assess the impact of the missing data, an additional set of analyses will be carried out using the complete case analysis (CCA), whereby results are analysed only for those participants who had both the completed cost and outcome data at all time points [29-32].

Long term cost and outcome projections

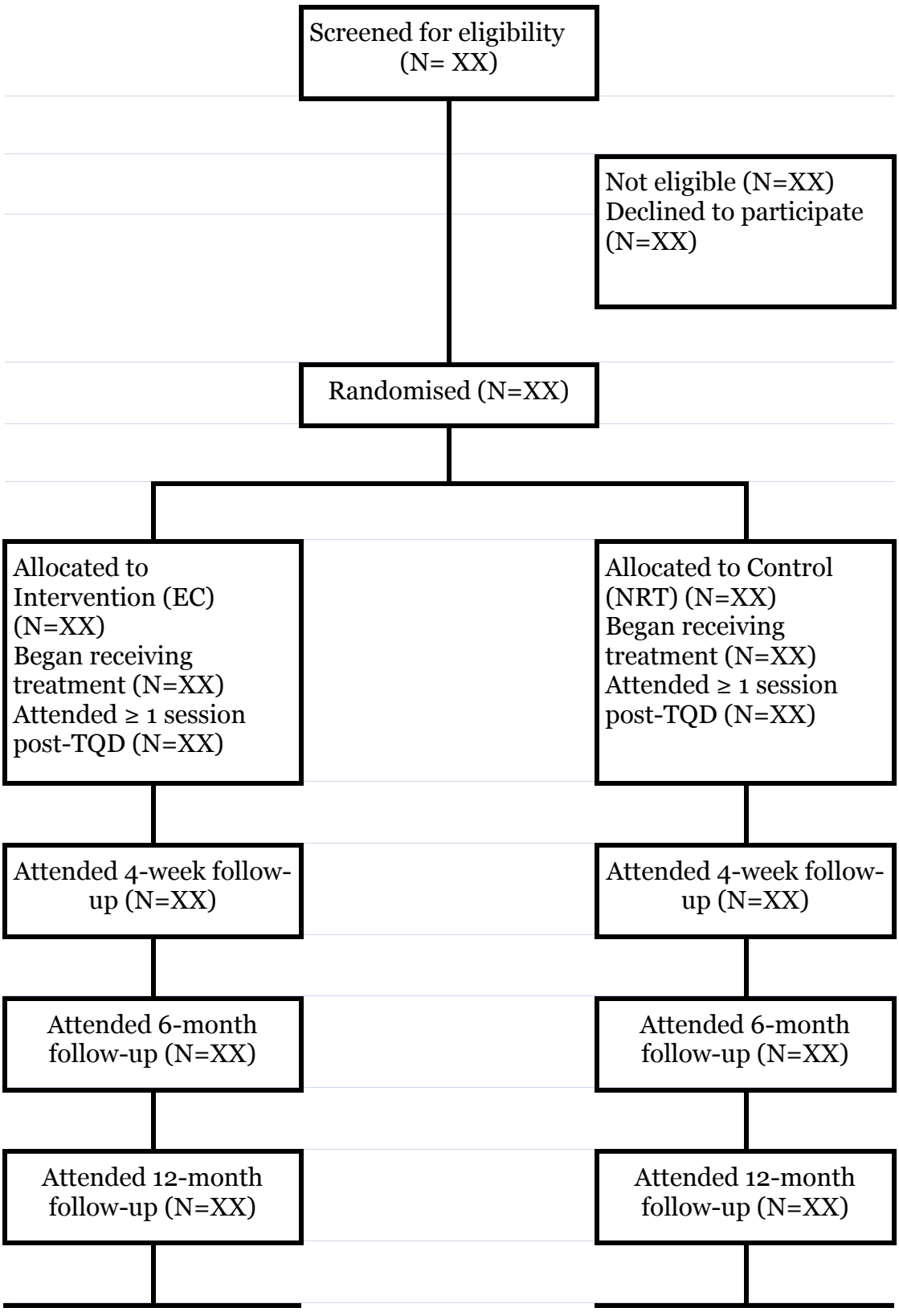
As the impact of smoking cessation is recognised to be life-long, we will investigate the use of existing models to project the impact of the intervention in a longer term. These models would enable the estimation of the potential long-term health care cost savings from smokers quitting smoking as a result of the intervention. These will be combined with longer term health utilities from published studies according to smoking status. The combination of trial data and health utility data will provide inputs to a longer term health economic model to estimate the longer term QALYs and cost per QALY gained.

Figures

Participant flow

Participant throughput will be summarized in a CONSORT diagram (see figure 1).

Figure 1: Consort Diagram



Patients included in the analysis for the primary outcome (N=XX) Participant deaths (N=XX) Participants who moved to untraceable address (N= XX) Participants who withdrew and refused follow up (N=XX) Participants who withdrew and permitted follow up (N=XX)	Patients included in the analysis for the primary outcome (N=XX) Participant deaths (N=XX) Participants who moved to untraceable address (N= XX) Participants who withdrew and refused follow up (N=XX) Participants who withdrew and permitted follow up (N=XX)

Survival curve

We will use Cox's proportional hazards model to compare time to relapse in the two conditions'.

Tables

Table 1 - Baseline measurements

	NRT (N=XXX)	EC (N=XXX)
Age (years) – mean (SD)		
Female – no. (%)		
Marital status – no. (%)		
Single		
Separated or divorced		
Married		
Widowed		
Ethnicity – no. (%)		
White British		
White other		
Black		
Asian		
Mixed		
Other		
Educational qualification – no. (%)		
Primary school		
Secondary school		
Further education/diploma		
Higher education		
Employment status – no. (%)		
In paid employment		
Entitled to free prescriptions – no. (%)		
Smoking and quitting history		
Cigarettes smoked per day – Mean (SD)		

Baseline CO – Mean (SD)		
FTCD – Mean (SD)		
Past use of stop smoking aids – N (%) Nicotine replacement therapy Champix Zyban Electronic cigarettes		
Age when started smoking – Mean (SD)		
Spouse or partner smokers – N (%)		
Study Site – no. (%)		
London		
Leicester		
East Sussex		

Table 2 – Participant adherence and contamination

	NRT (n=…)	**EC (n=…)**	**P value**	**Mean difference (95% CI)**
Number of contacts completed [a] (max 5 – preparation, W1, w4, 6M, 12M) – mean (SD)				
Use of allocated product over the initial **4 weeks:** On how many days used (0-28): Mean (SD) % using daily Use of allocated products **at 6M:** Length of allocated product use in weeks (0-26): Mean (SD) % using currently (at least once a week) Use of allocated products at **12M:** Length of allocated product use in weeks (0-26): Mean (SD) % using currently (at least once a week) Length of allocated product use in weeks (0-52) for those with complete 4 week, 6 and 12 month data: Mean (SD) Products used in those still using at 12M (type of NRT or type of EC) N (%)				
No. mls/cartridges/pieces/sprays of allocated product used per day – mean (SD) 1 week post quit 4 weeks post quit 24 weeks post quit 52 weeks post quit			N/A	

Tried non-allocated product within the **initial 4 weeks** N (%): Used for 5 or more consecutive days, N (%) Use of non-allocated products **at 6M (excludes initial 4 weeks):** Length of non-allocated product use in weeks (0-22): Mean (SD) Use of non-allocated products at **12M (excludes initial 4 weeks):** Length of non-allocated product use in weeks (0-22): Mean (SD) Length of non-allocated product use in weeks (0-48) for those with complete 6 and 12 month data: Mean (SD)				
Reason for stopping allocated product use in those not using it in the initial 4 weeks, N (%) Cost Did not like the taste Adverse reaction Not satisfying Difficult to use Embarrassing to use Difficult to obtain them Smoking normal cigarettes now To quit nicotine Other reason				
Any use of other products (including single use), N (%) Varenicline Bupropion				

[a] Includes those who completed and part completed sessions over the telephone

Table 3 – Choice of product

Type of NRT selected, N (%) Using combination, N (%)		
Switched to different NRT product in first 4 weeks N (%)		
Type of EC used (cartridge based or refillable), N (%) 1 week post quit 4 weeks post quit 24 weeks post quit 52 weeks post quit		
Switched to different EC in first 4 weeks N (%)		
E-liquid used		
Nicotine strength – mean (SD) 1 week post quit 4 weeks post quit 24 weeks post quit 52 weeks post quit		
Flavours, N (%) 1 week post quit 4 weeks post quit 24 weeks post quit 52 weeks post quit	Tobacco Fruit Menthol/mint Tobacco menthol Vanilla Chocolate, dessert. Sweet or candy flavor No flavor Coffee Alcoholic drink Energy or soft drink Other Don't know	
Given additional e-liquid at 2 weeks post-TQD, N (%) **Purchased additional e-liquid at 2 weeks post-TQD, N (%)**		

Table 4 – Helpfulness, taste, and satisfaction of product

Rating	**EC (n=…)**	**NRT (n=…)**	**P value**	**Mean difference (95% CI)**
Helpfulness[a], mean (SD) 1 week post quit 4 weeks post quit				
Taste compared to normal cigarettes, mean (SD) 1 week post quit 4 weeks post quit				
Satisfaction compared to normal cigarettes, mean (SD) 1 week post quit 4 weeks post quit				

[a]Where 2 NRT products were used and rated, the average rating of the two was taken.

Table 5 – Results for primary and secondary outcomes – unadjusted, using chi-square test; adjusted, using binomial regression

	NRT (n=…)	**EC (n=…)**	**Unadjusted Relative Risk (95% CI)**	**Unadjusted P-value**	**Adjusted Relative Risk (95% CI)**	**Adjusted P-value**
Primary outcome						
CO validated sustained abstinence at 52 weeks post TQD, N (%)						
Secondary Outcomes						
CO validated sustained abstinence between 24 and 52 weeks post TQD, N (%)						
CO validated sustained abstinence at 4 weeks post TQD, N (%)						
Sustained abstinence at 24 weeks post TQD, N (%)						
7-day point prevalence at 4 weeks post TQD, N (%)						
7-day point prevalence at 24 weeks post TQD, N (%)						
7-day point prevalence at 52 weeks post TQD, N (%)						

Table 6 – Change in respiratory symptoms

	NRT (N=)		EC (N=)		**P-value**	**Odds Ratio (95% CI)**
	Baseline N (%)	12 months N (%)	Baseline N (%)	12 months N (%)		
Shortness of breath						
Wheezing						
Cough						
Phlegm						

Table 7– Percentage participants reporting an adverse reaction at least once

% (N) reporting Adverse Reaction	**EC**	**NRT**	**P-value**
Nausea			
Sleep disturbances			
Throat/mouth irritation			

Table 8 – Differences in urges to smoke at 1 and 4 weeks post quit (abstainers only)

Symptom	**1 week post quit**		**P-value**	**Mean difference (95% CI)**	**4 weeks post quit**		**P-value**	**Mean difference (95% CI)**
	EC	NRT			EC	NRT		
Frequency of urge to smoke – mean (SD)								
Strength of urge to smoke – mean (SD)								
Composite urge score – mean (SD)								

Table 9 – Differences in urges to smoke at 1 and 4 weeks post quit (whole sample)

Symptom	**1 week post quit**		**P-value**	**Mean difference (95% CI)**	**4 weeks post quit**		**P-value**	**Mean difference (95% CI)**
	EC	NRT			EC	NRT		
Frequency of urge to smoke – mean (SD)								
Strength of urge to smoke – mean (SD)								
Composite urge score – mean (SD)								

Table 10 – Change in withdrawal symptoms between baseline and 4-weeks post TQD (abstainers only)

Symptom	**NRT (n=)**	**EC (n=)**	**P-value**	**Mean difference, (95% CI)**
Depressed – mean (SD)				
Irritable – mean (SD)				
Restless – mean (SD)				
Hungry – mean (SD)				
Poor concentration – mean (SD)				
Composite MPSS score – mean (SD)				

Table 11 – Change in withdrawal symptoms between baseline and 4-weeks post TQD (whole sample)

Symptom	**NRT (n=)**	**EC (n=)**	**P-value**	**Mean difference (95% CI)**
Depressed – mean (SD)				
Irritable – mean (SD)				
Restless – mean (SD)				
Hungry – mean (SD)				
Poor concentration – mean (SD)				
Composite MPSS score – mean (SD)				

Health economics tables

Table 12: Breakdown of intervention cost (mean [S.D.])

Cost item	NRT (n=xxx)	EC (n=xxx)
Behavioural support sessions		
NRT/EC supplies		
Information sheets		
Total		

Table 13: Unit cost

Services	Unit cost	Sources
Smoking cessation help		
GP		
NHS SSS		
NHS Smoking Helpline service		
Pharmacotherapies		
Patch		
Gum		
Microtab		
Inhaler		
Lozenge		
Spray		
Mouthstrip		
Varenicline		
Bupropion		
Health resources use		
A & E		
Outpatient		
Inpatient		
Day case		
Emergency ambulance		

GP (in office)		
Practice nurse (in office)		
GP (home visit)		
Practice nurse (home visit)		
Prescription		

Table 14: Usage and mean cost of services (mean [S.D.])

Services	NRT			EC		
	Baseline	Six months	12 months	Baseline	Six months	12 months
Smoking cessation help	n=xxx	n=xxx	n=xxx	n=xxx	n=xxx	n=xxx
GP						
NHS SSS						
NHS Smoking Helpline service						
Cost of smoking cessation help	*£xx (£xx)*	*£xx (£xx)*	*£xx (£xx)*	*£xx (£xx)*	*£xx (£xx)*	*£xx (£xx)*
Pharmacotherapies	n=xxx	n=xxx	n=xxx	n=xxx	n=xxx	n=xxx
Patch						
Gum						
Microtab						
Inhaler						
Lozenge						
Spray						
Mouthstrip						
Varenicline						
Bupropion						
Cost of pharmacotherapies	*£xx (£xx)*	*£xx (£xx)*	*£xx (£xx)*	*£xx (£xx)*	*£xx (£xx)*	*£xx (£xx)*
Health resources use	n=xxx	n=xxx	n=xxx	n=xxx	n=xxx	n=xxx
A & E						
Outpatient						
Inpatient						
Day case						
Emergency ambulance						

GP (in office)						
Practice nurse (in office)						
GP (home visit)						
Practice nurse (home visit)						
Prescription						
Cost of health resources use	*£xx (£xx)*	*£xx (£xx)*	*£xx (£xx)*	*£xx (£xx)*	*£xx (£xx)*	*£xx (£xx)*

Table 15: Utility values derived from EQ-5D (mean [S.D.])

	NRT		EC	
Baseline	n=xxx		n=xxx	
Six months	n=xxx		n=xxx	
12 months	n=xxx		n=xxx	

Table 16: Missing data table for imputation

Variables	Number of missing values	Proportion of missing values
Age		
Gender		
Study site		
Entitlement of free prescriptions		
Ethnicity		
Baseline FTCD		
Baseline smoking cessation help cost		
Six months smoking cessation help cost		
12 months smoking cessation help cost		
Baseline pharmacotherapies cost		
Six months pharmacotherapies cost		
12 months pharmacotherapies cost		
Baseline health resources cost		
Six months health resources cost		
12 months health resources cost		
Intervention cost		
Baseline EQ-5D index		
Six months EQ-5D index		
12 months EQ-5D index		

12 months validated abstinence		

Table 17: Basecase result (mean [S.E.] / [95% CI])

	NRT (n=xxx)	EC (n=xxx)
Intervention cost		
Smoking cessation help cost in the six months prior to baseline		
Pharmacotherapies cost in the six months prior to baseline		
Health resources use cost in the six months prior to baseline		
Health care cost in the six months prior to baseline		
Smoking cessation help cost in the six months post quit date		
Pharmacotherapies cost in the six months post quit date		
Health resources use cost in the six months post quit date		
Health care cost in the six months post quit date		
Smoking cessation help cost from six months to 12 months post quit date		
Pharmacotherapies cost from six months to 12 months post quit date		
Health resources use cost from six months to 12 months post quit date		
Health care cost from six months to 12 months post quit date		
Total costs during the trial period		
Unadjusted difference in total costs during the trial period		

Adjusted difference in total costs during the trial period		
EQ-5D index at baseline		
EQ-5D index at six months post quit date		
EQ-5D index at 12 months post quit date		
QALYs during the trial period		
Unadjusted difference in QALYs during the trial period		
Adjusted difference in QALYs during the trial period		
ICER at 12 months post quit date		

Table 18: Complete case analysis results (mean [S.D.] / [95% CI])

	NRT (n=xxx)	EC (n=xxx)
Intervention cost		
Smoking cessation help cost in the six months prior to baseline		
Pharmacotherapies cost in the six months prior to baseline		
Health resources use cost in the six months prior to baseline		
Health care cost in the six months prior to baseline		
Smoking cessation help cost in the six months post quit date		
Pharmacotherapies cost in the six months post quit date		
Health resources use cost in the six months post quit date		
Health care cost in the six months post quit date		

Smoking cessation help cost from six months to 12 months post quit date		
Pharmacotherapies cost from six months to 12 months post quit date		
Health resources use cost from six months to 12 months post quit date		
Health care cost from six months to 12 months post quit date		
Total costs during the trial period		
Unadjusted difference in total costs during the trial period		
Adjusted difference in total costs during the trial period		
EQ-5D index at baseline		
EQ-5D index at six months post quit date		
EQ-5D index at 12 months post quit date		
QALYs during the trial period		
Unadjusted difference in QALYs during the trial period		
Adjusted difference in QALYs during the trial period		
ICER at 12 months post quit date		

Table 19: Participants out-of-pocket cost (mean [S.D.])

	NRT (n=xxx)	EC (n=xxx)
E-cigarettes		
Pharmacotherapies		
Total costs to the NHS		

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Appendix 1

Timing of data collection

See attached CRF, version 5.0, 15 February 2017.

Appendix 2

Scoring of questionnaires

Fagerstrom Test of Cigarette Dependence

Screening and session 1 – baseline questions

Question	**Scoring**
Q7 On average, how many cigarettes do you usually smoke each day?	≤ 10 = 0 11 – 20 = 1 21 – 30 = 2 ≥ 31 = 3
Q8 How soon after waking up do you usually smoke?	Within 5 mins = 3 6-30 mins = 2 31-60 mins = 1 After 1 hour = 0
Q9 Do you find it difficult not to smoke in places where smoking is not allowed?	Yes = 1 No = 0
Q10 Do you smoke more during the first hours after waking than the rest of the day?	Yes = 1 No = 0
Q11 Which cigarette would you hate most to give up?	The first of the morning = 1 Another one = 0
Q12 Do you smoke if you are so ill that you are in bed most of the day?	Yes = 1 No = 0
Total (out of 10)	

Appendix 3

Data source for each outcome

1. CO validated sustained abstinence at 52 weeks post TQD	***Definition:*** At 52 weeks, no more than 5 cigarettes smoked since 2 weeks post TQD accompanied by a CO reading of < 8ppm at week 52. ***Data source: Q+3, Q+4, Q+24 and Q+52 CRF*** ***At Q+3, Q+4 and Q+24:*** ***Q3. Have you smoked regular cigarettes at all since your last visit/contact?*** 1. Not a single puff 2. Just a few puffs 3. ≤ 5 cigs in total 4. > 5 cigs in total 5. Currently quit – no other info (shown at Q+4, 24 and 52 only) NB. As per definition in primary outcome section, where data is missing for any of the above sessions participants will be assumed to be abstinent at 52 weeks providing they report no more than 5 cigarettes smoked since 2 weeks post TQD at 52 weeks accompanied by a CO reading of < 8ppm at week 52. ***Q2 (CO reading) on Q+4 post Quit CRF*** (only for those who attended Q+4 in person and self-reported abstinence). NB. As per definition in primary outcome section, those who do not provide a CO reading at 4 weeks post TQD but self-report abstinence at this time point will be assumed to be abstinent at 52 weeks follow up providing they report no more than 5 cigarettes smoked since 2 weeks post TQD at 52 weeks accompanied by a CO reading of < 8ppm at week 52. Those who self-report abstinence at 4 weeks post TQD but fail CO validation at 4 weeks post TQD (> 8ppm) will **not** be counted as abstinent at 52 week follow up. ***At Q+52:*** ***Q3.* Since two weeks after your quit date, have you smoked regular cigarettes at all?** (circle ONE) 1. Not a single puff 2. Just a few puffs 3. ≤ 5 cigs in total 4. > 5 cigs in total

	NB. as per definition in primary outcome section, where a participant reports smoking 1-5 cigarettes at more than one session/follow up but reports smoking no more than 5 cigarettes in total since 2 weeks post TQD at 52 week follow up, they will be assumed to have smoked no more than 5 cigarettes in total since 2 weeks post TQD and will meet the primary outcome definition providing their self-report is validated by a CO reading of <8ppm at the 52 week follow up. Where a participant reports being 'currently quit' at 52 week follow up, but has not been contactable to provide any other information, they will be not counted as a 52 weeks sustained abstainer since they will not have been contactable to arrange a CO validation. Where a participant reports being 'currently quit' at 4 and/or 24 weeks post TQD and has not been contactable to provide further information at these time points, but then reports smoking no more than 5 cigarettes in total since 2 weeks post TQD at 52 week follow up, they will be assumed to have smoked no more than 5 cigarettes in total since 2 weeks post TQD and will meet the primary outcome definition providing their self-report is validated by a CO reading of <8ppm at the 52 week follow up. ***Q+52 Validation Visit CRF*** **2. Record carbon monoxide in expired breath (ppm)**
Secondary Outcomes	
1. CO validated sustained abstinence between 24 and 52 weeks post TQD	***Definition:*** No more than 5 cigarettes smoked between weeks 24 and 52 accompanied by a CO reading of < 8ppm at week 52. ***Data source: Q+52 CRF*** **Have you smoked regular cigarettes at all in the last 6 months?** (circle ONE) 1. Not a single puff 2. Just a few puffs 3. ≤ 5 cigs in total 4. > 5 cigs in total 5. Currently quit – no other info NB. Where a participant reports being 'currently quit' at 52 week follow up, but has not been contactable to provide any other information, they will be not counted as a 24-52 week sustained abstainer since they will not have been contactable to arrange a CO validation.

Q+52 Validation Visit CRF
3. Record carbon monoxide in expired breath (ppm)

2. CO validated sustained abstinence at 4 weeks post TQD

Definition: Not a single puff of a cigarette in the last 2 weeks at 4 week follow up accompanied by a CO reading of < 8ppm at 4 week follow up.

Data source: Q+3 and Q+4 CRF
Q3. Have you smoked regular cigarettes at all since your last visit/contact? (circle ONE)

1. Not a single puff
2. Just a few puffs
3. ≤ 5 cigs in total
4. > 5 cigs in total
5. Currently quit – no other info (shown at Q+4, 24 and 52 only)

NB. As per the definition in the secondary outcomes section, where a participant misses Q+3 but reports not a single puff since their last visit at 4 weeks post TQD, accompanied by a CO reading of < 8ppm at 4 weeks, they will be counted as a CO validated abstainer at 4 weeks post TQD.

Where a participant reports being 'currently quit' at 4 weeks post TQD, but has not been contactable to provide any other information, they will not be counted as a 4 week abstainer since they will not have been contactable to arrange a CO validation.

Q2. Record carbon monoxide in expired breath (ppm) on Q+4 post quit CRF only

3. Sustained abstinence at 24 weeks post TQD

Definition: No more than 5 cigarettes smoked since 2 weeks post TQD at 24 weeks

Data source: Q+3, Q+4 and Q+24 CRF
Have you smoked regular cigarettes at all since your last visit/contact? (circle ONE)

1. Not a single puff
2. Just a few puffs
3. ≤ 5 cigs in total
4. > 5 cigs in total
5. Currently quit – no other info (shown at Q+4, 24 and 52 only)

NB. As per definition in secondary outcome section, where data is missing for 3 and/or 4 weeks post TQD participants will be assumed to be abstinent at 24 weeks post TQD providing they report no more than 5 cigarettes smoked since their last visit at 24 weeks.

Where a participant reports smoking 1-5 cigarettes at 3 and 4 weeks post TQD but reports smoking no more than 5 cigarettes in total since their last visit at 24 weeks, they will be assumed to have smoked less than 5 cigarettes in total since 2 weeks post TQD at 24 weeks.

Where a participant reports being 'currently quit' at 24 weeks post TQD, but has not been contactable to provide any other information, they will be counted as having smoked no more than 5 cigarettes since their last visit, and included as a 24 week sustained abstainer.

4. 7-day point prevalence at 4-weeks post TQD

Definition: Not a single puff in the last 7-days

Data source: Q+4 CRF
If you have smoked since your last visit/contact, did you smoke at all in the last 7 days?

1. Yes
2. No

5. 7-day point prevalence at 24-weeks post TQD

Definition: Not a single puff in the last 7-days

Data source: Q+24 CRF
If you have smoked since your last visit/contact, did you smoke at all in the last 7 days?

1. Yes
2. No

6. 7-day point prevalence at 52-weeks post TQD

Definition: Not a single puff in the last 7-days

Data source: Q+52 CRF
Have you smoked at all in the last 7 days?

1. Yes
2. No

7. Smoking reduction in participants who did not achieve abstinence at 52 weeks

Definition: Daily cigarette consumption of at least 50% of baseline consumption accompanied by a CO reading of 50% of baseline

Data source: Q+52 Post Quit CRF
3b. How many cigarettes per day are you smoking now?
3c. Percentage reduction in number of cigarettes smoked from start of study

Q+52 Validation Visit CRF
3. Record carbon monoxide in expired breath (ppm)

NB. Where participants have CO<10 at baseline and report 50% or more cigarette per day reduction at 52 weeks post TQD, sensitivity analyses will be carried out including and excluding them.

A sub-analysis of self-reported daily cigarette consumption at 52 week follow up reduced by at least 50% of baseline consumption without accompanied CO readings will also be conducted.

Data source: Q+52 Post Quit CRF
3b. How many cigarettes per day are you smoking now?
3c. Percentage reduction in number of cigarettes smoked from start of study

8. Changes in urges to smoke and other tobacco withdrawal symptoms at 1 and 4 weeks.

Definition: Differences in the ratings of urge frequency at 1 and 4 weeks post quit on following scale: not at all, a little of the time, some of the time, a lot of time, almost all of the time, all of the time.

Differences in the ratings of urge strength at 1 and 4 weeks post quit on following scale: no urges, slight, moderate, strong, very strong, extremely strong.

Data source: Q+1 and Q+4 Post Quit CRF

Q6. How much of the time have you felt the urge to smoke over the past week?

1. Not at all
2. A little of the time
3. Some of the time
4. A lot of the time
5. Almost all of the time
6. All of the time

Q7. How strong have these urges been?

1. No urges
2. Slight
3. Moderate
4. Strong
5. Very strong
6. Extremely strong

Definition: Changes in withdrawal symptoms between baseline and 4 weeks on following scale: not at all, slightly, somewhat, very, extremely.

Data source: Q+1 and Q+4 Post Quit CRF,

Q5. For each of the following (depressed, hungry, irritable, poor concentration, restless) rate how you have been feeling over the past week:

1. Not at all
2. Slightly
3. Somewhat
4. Very
5. Extremely

9. Treatment ratings

Definition: Ratings of helpfulness on the following scale: not at all, slightly, somewhat, very, extremely

Data source: Q+1 and Q+4 post quit CRFs
Q8c. Since your last visit/contact how helpful did you find your allocated product(s) in keeping you away from normal cigarettes?
1. Not at all
2. Slightly
3. Somewhat
4. Very
5. Extremely

Definition: Ratings of taste on the following scale: much worse than normal cigarettes, a little worse than normal cigarettes, the same as normal cigarettes, a little better than normal cigarettes, much better than normal cigarettes

Data source: Q+1 and Q+4 post quit CRFs
Q10. How good did it taste?
1.much worse than normal cigarettes
2. a little worse than normal cigarettes
3. the same as normal cigarettes
4. a little better than normal cigarettes
5. much better than normal cigarettes

Definition: Ratings of satisfaction on the following scale: much worse than normal cigarettes, a little worse than normal cigarettes, the same as normal cigarettes, a little better than normal cigarettes, much better than normal cigarettes

Data source: Q+1 and Q+4 post quit CRFs
Q11. How satisfying was it?
1. Much less than normal cigarettes
2. A little less than normal cigarettes
3. The same as normal cigarettes
4. A little more than normal cigarettes
5. Much more than normal cigarettes

10. Adverse reactions (AR)	***Definition: % (N) reporting 'Yes' to adverse reaction on at least one post quit session.*** ***Data source: Health Problems CRF checklist at all post quit sessions*** *(specifically nausea, sleep disturbance and throat/mouth irritation questions).*
11. Change in respiratory problems	***Definition:*** **Participants are defined as experiencing the health problem if they responding 'Yes' to it and the given time point.** ***Data source: Health Problems CRF checklist*** *(specifically shortness of breath, wheezing, cough and phlegm questions) at baseline and Q+52.*