TRIAL PROTOCOL

Effectiveness of **E**lectronic **C**igarettes compared with combination nicotine replacement therapy for smoking cessation in patients with chronic obstructive pulmonary disease **A**nd effect on **L**ung health (ECAL trial)

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2013)

Version Number: **3.0**

Version Date: **05-Jun-2025**

PROTOCOL DEVELOPMENT

Protocol amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
SA_01	20_Dec_2023	2.0	Substantial	Revisions made for utilisation of centralised stop smoking service/ pharmacy for distribution of NRT/ E-Cigs.
NSA01	20-Feb-2024	2.1	Non-Substantial	Correction of typos and make minor clarifications i.e. change to 'withdrawal' rather than 'change of status' form Correction made to AE reporting period to outline it is '26 weeks after agreed target quit day/ default target quit day' rather than 'after randomisation'
NSA03	24-Jul-2024	2.2	Non-Substantial	Correction to typos and addition of URL for trial database. Clarifications made to section regarding PICs Removal of Deputy CI information (at request of NIHR) Edits made for clarity in section 8.1 and 8.5.1
SA_02	05-Jun-2025	3.0	Substantial	· Update to Sponsor representative and address · Modification of the trial inclusion criteria · Removal of exclusion criteria for people using other stop smoking medications · Removal of requirement for 8-week wash out for COPD exacerbation or inpatient hospital stay · Edit made to recruitment methods to allow for sites to call patients to invite/ remind them about the trial. Wording change to allow flexibility with pre-

				baseline being done by either the research site or BCTU. · Edit made so patients can phone the BCTU trial office (in addition to current ability to email) · Information added to allow additional recruitment methods i.e. social media, Be Part of Research Volunteer Service (BPORVS) and wider care settings, i.e. community organisations and charities · Use of a translation service

Funding and support in kind	
Funder(s)/Supporting Organisations	**Financial and non-financial support given:**
National Institute for Health and Care Research (NIHR)	Financial
Funding scheme (if applicable)	Health Technology Assessment (HTA) Programme: £1,901,832.50 Efficacy and Mechanisms Evaluation (EME) programme: £330.455.18
Funder's reference number	HTA - NIHR129593 EME - NIHR131600
The Funders of the trial have had no role in the trial design, data collection, data analysis or data interpretation. This project is funded by NIHR Health Technology Assessment (HTA) programme and Efficacy and Mechanisms Evaluation (EME) programme. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.	

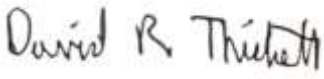
PROTOCOL SIGN OFF

Chief Investigator (CI) signature page

I, the Chief Investigator, confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as stated in this and any subsequent approved protocol will be explained.

Trial name:	ECAL Trial
Protocol version number:	Version: 3.0
Protocol version date:	30-Jun-2025
CI name:	Prof David Thickett
Signature and date:	 30-Jun-2025

Sponsor statement

By signing the IRAS form for this trial, University of Birmingham, acting as sponsor, confirm approval of this protocol.

Compliance statement

This protocol describes the ECAL trial only. The protocol should not be used as a guide for the treatment of patients not taking part in the ECAL trial.

The trial will be conducted in compliance with the approved protocol, the UK Policy Framework for Health and Social Care Research, Medicines for Human Use (Clinical Trials) Regulations 2004, Data Protection Act 2018 and the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031) and subsequent amendments thereof. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Principal Investigator (PI) signature page

As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise participant safety.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Trial name: Protocol version number:	ECAL trial Version: 3.0
Protocol version date:	05-Jun-2025
PI name:	
Name of Site:	
Signature and date:	_____ __ __ / __ __ / __ __ __ __

ADMINISTRATIVE INFORMATION

Reference Numbers	
Sponsor number	RG_20_120
ISRCTN reference number	82413824
IRAS reference number	1006828

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ABBREVIATIONS

Abbreviation	Term
ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
AR	Adverse Reaction
ARTP	Association for Respiratory Technology & Physiology
ATS	American Thoracic Society
BCTU	Birmingham Clinical Trials Unit
BNF	British National Formulary
BTS	British Thoracic Society
CAT	COPD Assessment Test
CCQ	Clinical COPD Questionnaire
CI	Chief Investigator
CO	Carbon Monoxide
CONSORT	Consolidated Standards Of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRN	Clinical Research Network
CTA	Clinical Trials Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CVD	Cardiovascular Disease
DCF	Data Clarification Form
DMC	Data Monitoring Committee
DNA	Did Not Attend
DSUR	Development Safety Update Report
EC	Electronic cigarette
ECAL	Trial acronym (Effectiveness of E-cigarettes And Lung health)
EME	Efficacy and Mechanisms Evaluation programme
EQ-5D-5L	EuroQol 5 dimensions, 5 level questionnaire
ERS	European Respiratory Society
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FBC	Full blood count

FEV1	Forced Expiratory Volume-one second
FTND	Fagerstrom Test for Nicotine Dependence
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General practitioner
HADS	Hospital anxiety and depression scale
HEAP	Health economics analysis plan
HRA	Health Research Authority
HTA	Health Technology Assessment programme
ICF	Informed Consent Form
IL	Interleukin
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
L	Litres
MA	Marketing Authorisation
MDC	Minimum Data Collection
MHRA	Medicines and Healthcare products Regulatory Agency
MMEF	Mean mid-expiratory flow
MPSS	Mood and Physical Symptoms Score
NHS	National Health Service
NHS R&D	National Health Service Research and Development
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NRT	Nicotine replacement therapy
PI	Principal Investigator
PIC	Patient Identification Centre
PIS	Participant Information Sheet
ppm	Part per million
QALY	Quality Adjusted Life-Year

QEHB	Queen Elizabeth Hospital, Birmingham
QMUL	Queen Mary University of London
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGT	University of Birmingham Research Governance team
RR	Relative risk
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SRNT	Society for Research on Nicotine and Tobacco
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNF	Tumour Necrosis Factor
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TQD	Target quit date
UK	United Kingdom
UKSBM	UK Society for Behavioural Medicine
UHB	University Hospitals Birmingham NHS trust
UoB	University of Birmingham
W	Weeks
WBC	White blood cell

TRIAL SUMMARY

Title Effectiveness of Electronic Cigarettes compared with combination nicotine replacement therapy for smoking cessation in patients with chronic obstructive pulmonary disease And effect on Lung health (ECAL Trial).

Objectives Among patients with chronic obstructive pulmonary disease (COPD):

1. **Main trial** - What is the effectiveness and cost effectiveness of e-cigarettes (ECs) compared with combination nicotine replacement therapy (NRT) as an aid to smoking cessation?
2. **Lung health sub-study** - What is the effect of switching from smoking to exclusive EC use on clinical, physiological and cellular lung health measures compared with quitting smoking without vaping and continuing to smoke?
3. **Wellbeing sub-study** - What is the effect of switching from smoking to exclusive EC use on depression, anxiety and social quality of life compared with quitting smoking without vaping and continuing to smoke?

Trial Design Multicentre, phase III, two arm, randomised controlled trial (RCT) with health economic evaluation and nested cohort analyses. The trial has a 5-month internal pilot phase.

Patient population and sample size 1250 people with COPD (625 per arm)

Setting The trial will be conducted in approximately 20 NHS sites across the UK (secondary/ primary/ community settings). Potential participants will be identified directly by participating research sites. Participating research sites may also utilise Patient Identification Centres (PIC) to identify potentially eligible patients.

Key Eligibility Criteria

Inclusion Criteria:

1) COPD diagnosis confirmed by post-bronchodilator spirometry (FEV_1/FVC <0.7), any GOLD stage
2) Current daily smoker
3) Willing to try to stop smoking using only allocated trial products
4) Aged 35 or over

Exclusion Criteria:

1) Unable to perform spirometry to a satisfactory standard (e.g. due to dementia, lack of teeth, lack of coordination or not having a good oral seal)
2) Deemed as unsuitable to participate in the trial (e.g. terminal illness, unable to give informed consent)
3) Unable to participate in behaviour support calls
4) Severe angina or unstable cardiovascular disease
5) History of end stage kidney disease
6) History of cirrhosis of the liver
7) Currently taking part in another trial of smoking cessation or COPD treatment/management
8) Contraindications to spirometry within the last 12 weeks – tuberculosis infection, cardiac infarction, retinal detachment, Pneumothorax or surgery on the chest, abdomen, brain, ears or eyes (invite back and re-assess after 12 weeks)

Participants will be individually randomised in a 1:1 ratio to either:

Intervention arm (EC): an EC Starter kit + initial supply of e-liquid. Participants in the intervention arm will be offered weekly telephone behavioural support up to 4 weeks post quit.

Comparator arm (NRT): up to 12-week supply of combination NRT (e.g. patch + fast acting NRT product). Participants in the comparator arm will also be offered weekly telephone behavioural support up to 4 weeks post quit.

Trial length and participant involvement period
Each participant will participate in the trial for approximately 52 weeks.

Outcome Measures (also see appendix 1)
n.b. all follow up points are calculated from target quit date (TQD)

1. Trial Primary Outcome:
Abstinence from smoking since TQD biochemically validated (exhaled CO<8ppm) at 52 weeks post TQD, defined in accordance with the Russell Standard[1]

2. Trial Secondary Outcomes:
1. Abstinence from smoking for at least 26 weeks biochemically validated (exhaled CO<8ppm) at 52 weeks
2. 7-day point prevalence abstinence from smoking biochemically validated (exhaled CO<8ppm) at 52 weeks
3. Self-reported abstinence from smoking for at least 26 weeks at 52 weeks
4. Self-reported 7-day point prevalence abstinence from smoking at 4, 26 and 52 weeks
5. Reduction in cigarettes smoked (self-report of any and > 50% reduction from baseline to 52 weeks, confirmed by reductions in expired CO readings at 52 weeks)
6. Reduction in cigarettes smoked (self-report of any and > 50% reduction from baseline to 26/52 weeks)
7. Continued use of allocated product at 4, 26 and 52 weeks
8. Withdrawal symptoms and urges to smoke (change from baseline to 1/2/3/4 weeks) measured using the mood and physical symptom scale (MPSS)
9. COPD Symptoms (change from baseline to 4/26/52 weeks) measured using COPD Assessment Test (CAT) and the Clinical COPD Questionnaire (CCQ)
10. Number of COPD exacerbations over the past 52 weeks (from baseline to 52 weeks)
11. Number of self-reported upper respiratory tract infections over the past 52 weeks (from baseline to 52 weeks)
12. Post bronchodilator spirometry (FEV_1, FVC and MMEF change from baseline to 52 weeks).
    - Forced Expiratory Volume in 1 Second (FEV_1)
    - Forced Vital Capacity (FVC)
    - Mean Mid-Expiratory Flow (MMEF)

3. Health economic outcomes:
1. Health-related quality of life (EQ-5D-5L) (change from baseline to 4/26/52 weeks)
2. Use of healthcare resources and costs (measured at 26 and 52 weeks)
3. Cost-effectiveness based on cost per quitter and cost per Quality-Adjusted Life-Year (QALY) at 52 weeks post TQD, and modelled cost per QALY over patient lifetime

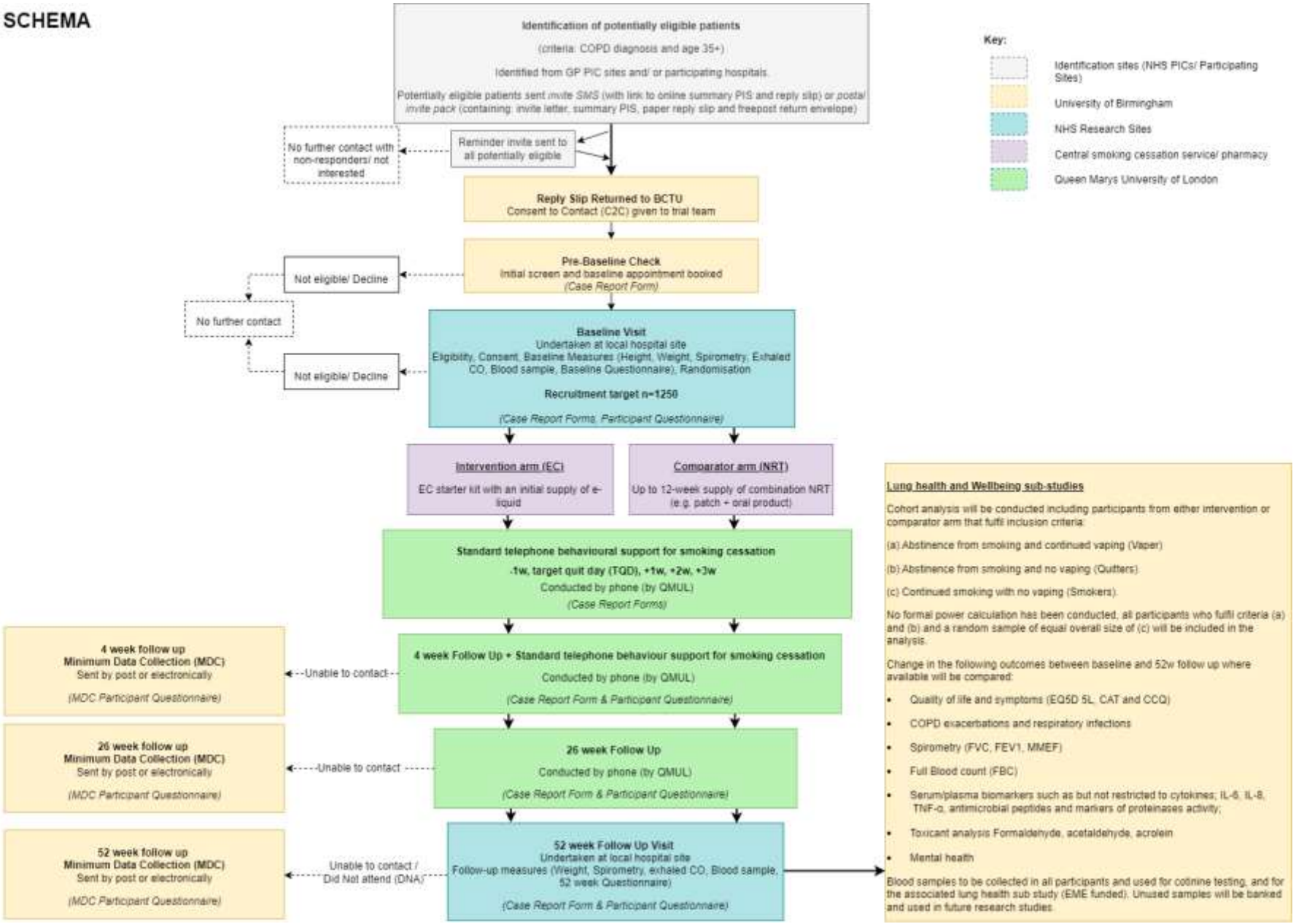
4. Lung health sub-study outcomes (in participants included in the cohort analysis only):

1. COPD Symptoms (change from baseline to 4/26/52 weeks) measured using COPD Assessment Test (CAT) and the Clinical COPD Questionnaire (CCQ)
2. Health-related quality of life (EQ-5D-5L) (change from baseline to 4/26/52 weeks)
3. Number of COPD exacerbations over the past 52 weeks (from baseline to 52 weeks)
4. Number of self-reported upper respiratory tract infections over the past 52 weeks (from baseline to 52 weeks)
5. Post bronchodilator spirometry (FEV_1, FVC and MMEF change from baseline to 52 weeks
   - Forced Expiratory Volume in 1 Second (FEV_1)
   - Forced Vital Capacity (FVC)
   - Mean Mid-Expiratory Flow (MMEF)
6. Full blood count (total and differential WBC $x10^9$/L) (change from baseline to 52 weeks)
7. Serum/plasma biomarkers such as but not restricted to cytokines IL-6, IL-8, TNF-α; antimicrobial peptides; and markers of proteinase activity (change from baseline to 52 weeks)
8. Toxicant analysis; to include toxicants such as formaldehyde, acetaldehyde, acrolein (change from baseline to 52 weeks)

5. Wellbeing sub-study outcomes (in participants included in the cohort analysis only):

1. Anxiety - HADS (change from baseline to 52 weeks)
2. Depression - HADS (change from baseline to 52 weeks)
3. Mixed anxiety and depression - EQ-5D-5L (change from baseline to 52 weeks)
4. Breathing related depression and social quality of life - CCQ (change from baseline to 52 weeks)

TRIAL SCHEMA



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1. BACKGROUND AND RATIONALE

1.1 Background

COPD and smoking Chronic obstructive pulmonary disease (COPD) is a common lung condition which affects around 2 million people in the United Kingdom (UK).[2] It is currently the fourth most common cause of death worldwide,[3] and death rates are rising. It is projected to become the leading cause of death worldwide by 2035.[4] Patients with this condition experience symptoms including breathlessness, cough, increased sputum production and acute periods of exacerbation of their symptoms which may lead to hospitalisation. Lung function (specifically airflow obstruction) defines disease severity with patients experiencing a decline as the disease progresses. In developed countries, cigarette smoking is the most common cause of COPD, and continued smoking by people with COPD is known to accelerate decline in lung function. Smoking cessation is the only known strategy that limits this acceleration[3], and therefore smoking cessation is a priority for these patients.

Guidance from the National Institute for Health and Care Excellence (NICE) recommends that COPD patients who are still smoking should be encouraged to quit at every opportunity and offered help to do so.[5] However, prevalence of smoking in COPD patients in the UK remains much higher than in the general population, with estimates as high as 35%.[6 7] COPD patients are generally more heavily addicted to smoking and find it harder to quit,[8] and experience disproportionately larger adverse health effects from their smoking than the general population.[9 10] Even when using effective NICE recommended treatments to support a quit attempt, success rates are low with over 80% relapsing within a year.[11 12]

Electronic cigarettes Electronic cigarettes (ECs) are commercially available products that vaporise a liquid which usually contains nicotine and is inhaled by the user.[13] They have emerged as a viable alternative to cigarette smoking, with considerable potential to replace and eventually eradicate conventional cigarettes.[14] In the UK in 2021, an estimated 3.6 million adults used ECs, and of these 2 million had completely stopped smoking.[15] Survey evidence shows that people with COPD are using ECs to help them stop smoking, however there remain unanswered questions regarding their effectiveness for smoking cessation and the potential effects of use on health in this patient group.

1.2 Previous literature

ECs for smoking cessation There are a number of systematic reviews assessing the effectiveness of ECs for smoking cessation, one of which is a Cochrane review.[16] The latest version of the Cochrane review found that nicotine ECs are more effective than nicotine replacement therapy (NRT) (Relative Risk (RR) 1.63, 95% Confidence Interval 1.30 to 2.04) for smoking cessation. These estimates were based on data from six trials.[16] Reviews acknowledge the need for additional high-quality studies testing ECs for smoking cessation against standard treatment (such as NRT), and no EC trials so far have been conducted in patients with COPD.

Effect of vaping on the lungs A number of systematic reviews [17-21] and reports commissioned by Public Health England/Office for Health Improvement and Disparities have reviewed the evidence on the effect of ECs on health. [13 22 23] However, to date, there are only a limited number of studies that have reported on the effect of EC use on clinical/physiological/cellular lung health outcomes in humans, see below. [24-26]

Clinical measures of lung health - respiratory symptoms, exacerbations and infections
Smoking increases the risk of chronic respiratory symptoms, and there is a decrease in symptoms in patients with COPD after smoking cessation.[27] Improvements in symptoms in quitters compared to continuing smokers have been reported in secondary analyses from smoking

cessation trials in COPD patients,[28] including The Lung Health Study.[27] Etter et al. demonstrated that cough, wheeze, breathlessness when climbing stairs, and sputum production improve rapidly after one month of smoking cessation in an internet sample of 252 COPD patients who quit smoking.[29]

There are limited data available about changes in COPD symptoms in people who quit smoking and switch to vaping. One study reported findings from an international cross-sectional study of 19,353 EC users recruited from online EC user forums, which included a sub group of 1062 COPD patients. The COPD patients were asked if they experienced any change in their condition after initiating EC use. The majority of patients (75.7%) reported an improvement, 12.7% reported that their COPD remained stable and 0.8% reported that they had experienced a worsening of their condition. This pattern of change was similar for former smokers, as well as those who were continuing to smoke, with 68.7% of current smokers also reporting improvements in their condition. [24] In our National Institute for Health and Care Research (NIHR) funded trial with general population smokers,[30] the EC arm participants reported significantly greater improvements in coughs and phlegm production than NRT arm participants, which remained significant after controlling for continued smoking.[30]

In terms of frequency of exacerbations in COPD, Polosa et al. reported significant improvements in exacerbation rates in 22 patients who regularly used EC over a three-year period compared to 22 age and sex matched controls. Nine of the 22 patients using ECs continued to smoke (dual use), reducing cigarette consumption by over 75%, and a significant reduction in exacerbation rate was still observed in this group of dual users at the end of the follow up period. [26] However, this study did not include a comparator group of people who quit smoking without vaping, so it is not possible to verify if exclusive vaping is as safe or beneficial as quitting smoking using other means.

In the general population, there is emerging evidence that vaping is also associated with a reduction in infection, including in non-smokers.[31-33] In a large internet survey, 66% of respondents reported a reduction in airway infections after switching from smoking to vaping. However, this remains to be confirmed and any improvements in symptoms/infections that are experienced by vapers need to be compared with any changes experienced by quitters who do not use ECs.

Physiological measures of lung health – FEV_1

It is well established that smoking leads to an accelerated decline in lung function in "susceptible" individuals, and that smoking cessation slows the rate of decline to that seen in non-smokers.[34] [35-37] To date (2022), there is evidence from one small retrospective cohort study of the effects of vaping on lung function. Polosa et al. found no significant difference in post-bronchodilator FEV_1 between baseline and 3 year follow up for patients who used ECs (n=22). However, the study is likely to be substantially underpowered and did not include comparison to patients who were complete abstainers. [26] There are therefore no current data available to assess if exclusive use of an EC is comparable to quitting smoking alone in terms of slowing the rate of decline in FEV_1.

Cellular measures of lung health – inflammatory markers and mediators

In vitro and lab-based human studies have reported both cytotoxic and acute inflammatory effects associated with vapour exposure to the lungs or lung cells,[38-41] including work conducted by our group.[38] A high number of inflammatory cells and mediators have been implicated in COPD pathogenesis. However, no known studies have been conducted in people who have already developed COPD to investigate how inflammatory markers/mediators change after

switching to vaping, and as with other lung health measures, studies have not compared changes in vapers to changes when people quit smoking without vaping. We will examine inflammatory markers and mediators which have the strongest evidence base for COPD pathogenesis that are raised in smoking and reduce with smoking cessation[42-45] to see if this is also seen when people with COPD switch to vaping.

Effect of vaping on mental health/wellbeing

A systematic review published in 2021 showed that there is an improvement in mental health after quitting smoking which starts to manifest from around 6 weeks after quitting smoking.[46] There are a number of reasons why mental health may improve after quitting smoking, such as the complete removal of nicotine from the system. However, other mechanisms have also been implicated such as a reduction in inflammation,[47] and it may be that no longer being subject to the health, economic and addictive effects of smoking may improve mental health/wellbeing. Studies are needed that assess what happens to mental health/wellbeing when people stop smoking and switch to vaping, [48] and this study will provide an opportunity to examine this in patients with COPD.

1.3 Trial rationale

1.3.1 Justification for participant population

There are currently (as of 2022) no trials testing the effectiveness of ECs in COPD patients. Prevalence of smoking is high in this patient group (~35%), and smoking cessation is crucial to changing the trajectory of the disease. Given that most people relapse back to smoking when using currently available treatments it is worthwhile investigating whether ECs are more effective than combination NRT for this patient group. It is also important to investigate how vaping affects lung health/wellbeing in comparison with continuing to smoke or quitting without the aid of an EC in this patient group with a pre-existing lung condition.

1.3.2 Justification for inclusion of pregnant women

The trial will not exclude pregnant women. Smoking in pregnancy is associated with increased risks of miscarriage, stillbirth, prematurity, low birth weight, perinatal morbidity and mortality, neo-natal and sudden infant death[49] and possibly also adverse infant behavioural outcomes.[50 51] A trial of nicotine patches [52 53] indicated that nicotine replacement is safe to use in pregnancy, and NICE guidelines recommend NRT to help women stop smoking during pregnancy and in the first year after childbirth.[54] A trial comparing EC and NRT during pregnancy showed safety outcomes were similar between the two study arms, apart from low birthweight (<2,500 g), which was less frequent in the e-cigarette arm. [55] Overall, when the choice is between using nicotine products such as NRT or e-cigarettes or continuing to smoke, the use of NRT or e-cigarettes is a recommended option.

1.3.3 Justification for design

To definitively test the effectiveness and cost-effectiveness of EC for smoking cessation compared with NRT in COPD patients, a randomised controlled trial (RCT) is required with embedded economic analysis.

To investigate the effect of switching to vaping on lung health and wellbeing, a cohort analysis is necessary. For the cohort analysis, participants will be re-grouped based on their smoking and vaping status throughout the trial into vapers, quitters or smokers, rather than being analysed by trial arm. This is necessary as many people in each arm of the trial will relapse back to smoking, and therefore analysis by trial arm will not show the effect of vaping, quitting or smoking on lung health/wellbeing as trial arms will contain a mixture of these.

1.3.4 Justification for choice of intervention

We will be using a modern EC starter pack which will include an initial supply of e-liquid. There is no recommended length of use of ECs for smoking cessation as is the case for NRT where up to 12 weeks is recommended. Participants will therefore be given an initial supply of a sufficient amount to start using the EC (up to 20 mg nicotine/ml) and then advised to source continuing supplies. Participants will be advised how to continue sourcing supplies according to preference which may include changing devices, flavours and strengths as needed. This strategy was used successfully in our previous trials.[30 55]

ECs will be compared with up to 12 weeks supply of combination NRT. Participants will be encouraged to use a nicotine patch in combination with a fast-acting product (e.g. gum, lozenge, microtab) as this has been shown to be the most effective way of using NRT[56] and is recommended by NICE.[54] Taking a pragmatic approach, should participants indicate they are not able to use the patch (e.g. due to previous reactions to nicotine patch), they will be able to choose two fast-acting products. Choice of fast-acting nicotine product for all participants will also be dependent on product availability.

1.3.5 Justification of choice of primary outcome

We will measure abstinence from smoking between target quit date (TQD) and 52 weeks (post TQD) as defined by the Russell standard,[1] which will be biochemically confirmed at 52 weeks with an exhaled CO reading of <8 part per million (ppm). This is the accepted way to measure smoking cessation in this research field and will enable findings to be compared across the literature and combined in future meta-analyses.[16]

2. AIMS AND OBJECTIVES

2.1 Internal pilot objectives

To investigate the feasibility of recruitment to the main trial. This will be assessed using the traffic light criteria as outlined in section 9.1.

2.2 Main trial and sub study objectives

2.2.1 Main trial aims and objectives

To investigate the effectiveness and cost effectiveness of ECs as an aid to smoking cessation compared with combination NRT in patients with confirmed COPD.

2.2.2 Lung health sub-study aims and objectives

To investigate the effect of switching from smoking to exclusive EC use on clinical, physiological and cellular lung health measures compared with (1) quitting smoking without vaping and (2) continuing to smoke in patients with COPD.

2.2.3 Wellbeing sub-study aims and objectives

To investigate the effect of switching from smoking to exclusive EC use on anxiety, depression and social quality of life compared with (1) quitting smoking without vaping and (2) continuing to smoke in patients with COPD.

3. TRIAL DESIGN AND SETTING

3.1 Trial design

The effectiveness and cost-effectiveness of ECs will be tested by conducting a national, multicentre, phase III, two arm RCT with internal pilot and economic evaluation. A target of 1250 participants will be recruited and randomised in a 1:1 ratio to either:

- Intervention (EC): EC Starter kit and initial supply of e-liquid; or
- Comparator (NRT): Up to 12 weeks of combination NRT (e.g., patch + oral product)

The trial includes two nested cohort studies assessing lung health and wellbeing.

The trial follow-up time points (and therefore outcome measures) will be established based on the TQD. If participants are unable to be contacted to set a TQD then a default TQD will be set (approximately 2 weeks after the baseline visit) for follow up time points to be based on. Participants will be followed up for 52 weeks post TQD.

3.2 Trial setting

The trial will be conducted in approximately 20 NHS sites across the UK (secondary/ primary/ community settings). Potential participants will be identified directly by participating research sites. Participating research sites may also utilise Patient Identification Centres (PIC) to identify potentially eligible patients.

Participants will undergo a baseline visit and 52-week follow-up visit at the NHS research site. During these visits all participants will be required to complete a questionnaire and CRF, provide an exhaled CO reading, spirometry reading and a blood sample. Behavioural support telephone calls (at -1, 0, +1, +2, +3 and +4-weeks post TQD) will be delivered to all participants over the phone or via video call by the Health and Lifestyle Research Unit at the Wolfson Institute of Population Health, Queen Mary University of London.

The 4 and 26-week follow up will also be conducted over the phone or via video call by the Health and Lifestyle Research Unit, if uncontactable a follow up questionnaire will be sent to the participant by post/email.

3.3 Sub-studies

In addition to the main RCT, there will be the following embedded cohort studies:

(1) Lung health sub-study
(2) Wellbeing sub-study

These will be conducted once all follow up is complete and the database is locked for analysis. For both of the cohort analyses, participants from the trial will be re-categorised into the following exposure groups based on their smoking and vaping status during the trial, assessed at 52 weeks:

- Vaper (switched to exclusive EC use)
- Smoker (continued to smoke)
- Quitter (quit smoking and did not vape)

For lung health, the analysis will compare change in clinical, physiological and cellular lung health measures and toxicant levels in vapers, smokers and quitters. Cellular and toxicant outcomes will be measured in blood samples taken from participants when they attend the research site at baseline and 52 weeks. As it is not possible to know which participants will fall into each of these exposure groups when the blood is taken, blood will be taken from all participants. Blood

samples not used will be banked for future studies (subject to participant consent). The blood measures have been funded by the NIHR EME funding stream.

For wellbeing, the analysis will compare change in anxiety, depression and social quality of life in vapers, smokers and quitters.

3.4 Assessment of risk

All clinical trials can be considered to involve an element of risk and in accordance with the Birmingham Clinical Trials Unit (BCTU) standard operating procedures this trial has been risk assessed to clarify any risks relating uniquely to this trial beyond that associated with usual care. A Risk Assessment has been conducted and concluded that this trial corresponds to the following categorisation: Type A = No higher than the risk of standard medical care.

This trial is considered to be a low-risk Clinical Trial of an Investigational Medicinal Product (CTIMP). Nicotine Replacement Therapy products constitute the IMP and will be used on-label. The EC is a consumer product regulated under the Tobacco and Related Product Regulations. We will be providing an EC starter pack to allocated participants, but they will be permitted within the trial to purchase a different EC device and/or e-liquid if the one provided does not work for them. This has worked in our previous trials and is the current approach used by stop-smoking services who provide EC starter packs as part of standard care and encourage clients to switch to other EC products if needed.

The wellbeing sub-study will utilise measures which assess depression and anxiety. This may identify people at risk i.e., a HADS scoring of ≥11 and/or may prompt disclosure of other mental health related issues of concern. The PI will be notified in these circumstances and local site process will be followed.

4. PATIENT IDENTIFICATION AND INVITATION

There are a number of methods available to identify potentially eligible patients and invite them to take part in the trial. This is to maximise the ability to recruit to the required target. These methods are summarised in table 1 and described in detail in the sections below.

Table 1: Summary of method options to identify potentially eligible patients, invite them to take part in the trial and complete the pre-baseline check

	Method of identification	Method of invitation and pre-baseline check
At a research site	Patient is approached face to face by direct care team	If the patient is interested in taking part in the trial they will complete the pre-baseline check face to face. The pre-baseline check will be conducted by the direct care team but can be supported by the BCTU trial office or QMUL trial team. Upon confirming the patient meets the minimum trial entry criteria, the patient will be booked in for the baseline appointment by the site Alternatively, a patient can be given an invitation pack (paper or online). If interested the patient will complete the reply slip (paper or online) which is sent to BCTU (by post or online) who will then contact the patient, or hand over to QMUL or relevant site to complete the pre-baseline check. Upon confirming the patient meets the minimum trial entry criteria, the patient will be booked in for the baseline appointment by the site.
	Patient sees advertisement and decides to express an interest	The advertisement will provide a link to the online invitation pack. If interested the patient will complete an online reply slip which is sent to BCTU. Patients who return a reply slip will be contacted by BCTU, QMUL or relevant site, to complete the pre-baseline check. Upon confirming the patient meets the minimum trial entry criteria, the patient will be booked in for the baseline appointment by the site. Alternatively, trial advertisements will provide the email & phone number for the trial office so patients can ask questions and express an interest directly, if they prefer. BCTU, QMUL or relevant site will complete the pre-baseline check. Upon confirming the patient meets the minimum trial entry criteria, the patient will be booked in for the baseline appointment by the site.
	Patient identified by other means (e.g. clinic lists/medical records)	Patients may receive a phone call inviting them to take part in the trial and/or will be sent an invitation pack by post (paper) or by text (online), by their direct care team. If interested the patient will complete the reply slip (paper or online) which is sent to BCTU (by post or online) who will then contact the patient, or hand over to QMUL or relevant site, to complete the pre-baseline check. Upon confirming the patient meets the minimum trial entry criteria, the patient will be booked in for the baseline appointment by the site. There will be a reminder invite or phone call after approximately 2 weeks.
At a patient identification Centre (PIC)	Patient sees advertisement and decides to express an interest	The advertisement will provide a link to the online invitation pack. If interested the patient will complete an online reply slip which is sent to BCTU. Patients who return a reply slip will be contacted by BCTU, QMUL or relevant site, to complete the pre-baseline check. Upon confirming the patient meets the minimum trial entry criteria, the patient will be booked in for the baseline appointment by the site.

		Alternatively, trial advertisements will provide the email and phone number for the trial office so patients can ask questions and express an interest directly, if they prefer. BCTU, QMUL or relevant site, will complete the pre-baseline check and upon confirming the patient meets the minimum trial entry criteria, the patient will be booked in for the baseline appointment by the site.
	Patient identified through clinic lists/medical records search	Patient is sent an invitation pack by post (paper) or by text (online) or approached in person by their direct care team. If interested the patient will complete the reply slip (paper or online) which is sent to BCTU (by post or online) who will then contact the patient, or refer to the QMUL or relevant site, to complete the pre-baseline check. Upon confirming the patient meets the minimum trial entry criteria, the patient will be booked in for the baseline appointment by the site. There will be a reminder invite or phone call after approximately 2 weeks.
Identification by self-referral	Patient approached and/or provided with information about the trial via social media, Be Part of Research Volunteer Service (BPORVS) and wider care settings, i.e. community organisations and charities	Information about the trial will be advertised/ promoted to members of the public and those who feel they meet the trial requirements will be able to self-refer into the trial by completing a reply slip (paper or online) which is sent to BCTU (by post or online) who will then contact the patient, or refer to the QMUL or relevant site, to complete the pre-baseline check and book the patient in for the baseline appointment. Where postal invites are sent a reminder letter or reminder phone call may be given after approximately 2 weeks.

4.1 Criteria for identifying potentially eligible patients

Patients will be considered potentially eligible for the trial if they meet the following criteria:

a. COPD diagnosis
b. Aged 35 or over
c. Current smoker (when identifying patients through search of medical records this will only be applied if there is relatively complete and recent data available on smoking status.)

4.2 Identification by research site

At the site, potentially eligible patients will be identified either by their direct care team or by the patients asking for/accessing trial information after seeing ethically approved advertising in clinical areas and/or websites and/or social media accounts. Those identified will either be directed to the site trial team who will conduct the pre-baseline check on the ECAL database and book the patient into a baseline appointment or they will have access to an invitation pack which may be on paper or online, or they can email or call BCTU directly.

In addition, the secondary care site team can identify potentially eligible patients through clinic lists/hospital records based on the criteria outlined in section 4.1, and those identified will be invited to take part in the trial, by their direct care team. This may be by phone, post (paper invitation pack) or by email/text (online invitation pack). Details of the invite process can be found in section 4.4.

4.3 Identification by PIC

Potential participants will be identified through centres (e.g. GP practices, pulmonary rehabilitation, targeted lung health check/ lung cancer screening) within a reasonable distance from participating research sites. The PIC will conduct clinic list/medical record system search(es) to identify potentially eligible patients based on the criteria outlined in section 4.1. The list(s) will be screened for potentially eligible patients to exclude those patients considered inappropriate to be invited to participate in the trial. Potential eligible patients will then be contacted by the PIC to invite them to take part in the trial. This invite may be by post or text and will provide an invitation pack which may be on paper or online, as appropriate for the contact method. Details of the invite process can be found in section 4.4.

In addition, the trial will be advertised using ethically approved promotional materials (i.e. posters and flyers) in the waiting rooms and/or websites and/or social media accounts of participating PIC. Patients who are interested in the trial will be able to express their interest by accessing the online invitation pack using the link provided or can contact the trial office directly via email or phone.

4.4 Identification by self-referral

The trial will be advertised/ promoted to members of the public using local/social media campaigns, Be Part of Research Volunteer Service (BPORVS) and wider care settings, i.e. community organisations (i.e. breatheasy groups) and charities. People who are interested can self-refer by completing either an online or paper reply slip or contacting the trial office directly via email or phone.

A mixture of all the recruitment methods specified above will proceed in parallel until the required sample size is reached.

4.5 Patient invitation to take part

Patients will receive either:

a. **Paper invitation pack** that will contain the trial invitation letter, Summary Participant Information Sheet (PIS) with link to the main PIS, reply slip and pre-paid return envelope.
b. **Online versions of invitation pack** that will contain access to the summary PIS, main PIS and a reply slip that can be returned electronically

Reply slips will collect the patients name and contact details and will be returned to BCTU. BCTU will then contact the patient to complete the baseline check and book patients into the baseline appointment (see section 4.5.2).

Where patients are approached face to face at site and are able to speak directly to the site trial team, or express an interest directly to BCTU, a consent to contact CRF will be completed (instead of a reply slip) and the patient will be given access the PIS either in paper or online, as appropriate as part of the pre-screening check (see section 4.5).

For patients sent an invitation by primary or secondary care after identification through medical records or clinic lists, a reminder invitation letter, text or call will give approximately 2 weeks after the initial invite. All potential participants identified in this way will receive the reminder regardless of whether or not they have returned their reply slip or expressed an interest directly. This will be made clear in the main PIS. The reminder invitation will acknowledge those who have already responded and ask them to ignore the reminder. If no response is received after this, the patient will be considered as not interested and will not be contacted again.

4.6 Strategy to improve inclusion

To enhance the trial's inclusivity, the trial team will offer access to a translation service (available by telephone, video, or in person) to assist with providing study information and behavioural support, in addition to questionnaire completion and data collection. Use of NHS translation services may be utilised at sites as needed. Additionally, participants are welcome to seek assistance from a friend or family member, if preferred.

4.7 Pre-baseline check and baseline appointment booking

Patients expressing an interest in the trial will proceed to a pre-baseline check and will have their baseline appointment booked if they pass the check. The purpose of the pre-baseline check is to reduce the chance of baseline appointments being scheduled for patients who are ineligible.

4.7.1 Conducted by research sites

Patients who are identified face to face at research sites will proceed straight to the pre-baseline check and baseline appointment booking at the site if they are able to. The information provided will be entered straight onto the ECAL database. This process will not involve BCTU.

The BCTU trial office may also allocate reply slips to a relevant site so the pre-baseline check and baseline appointment booking can be undertaken by site.

The pre-baseline check will include the following:

a) Provide the participant with the summary PIS and check they are interested in taking part
b) Discuss the trial with the patient
c) Answer any questions the patient has about the trial

d) If the patient is interested, complete a consent to contact form which will add the patient's contact details to the ECAL database (this is instead of the patient completing a reply slip as part of the invitation pack)
e) Go through the pre-baseline check criteria within the ECAL trial database (see section 4.6.3)
f) If eligible based on pre-baseline check, book the patient directly into the baseline clinic Notify the patient of their baseline appointment date/time, i.e. verbally, appointment card, SMS text, email or letter
g) Upon booking a baseline visit, the patient will be directed to view the main PIS on the trial website so they have time to read through ahead of their appointment.

4.7.2 Conducted by BCTU or QMUL

When a reply slip has been received by BCTU, or potentially eligible patients have contacted BCTU directly and a consent to contact CRF has been completed, the information will be entered on to the ECAL database. As the patient has actively opted to return the reply slip or express an interest directly and provided their name and contact information on it, this indicates consent for BCTU to contact them. It will explicitly state on the reply slip and consent to contact CRF that the patient's details will be stored on the ECAL database once received by BCTU.

BCTU or QMUL team will then contact the patient for the pre-baseline check. During the pre-baseline check, BCTU or QMUL will:

a) Discuss the trial with the patient
b) Answer any questions the patient has about the trial
c) Check that they are interested in taking part
d) Go through the pre-baseline check criteria within the ECAL trial database (see section 4.5.1)
e) If eligible based on pre-baseline check, book the patient into a baseline visit at their nearest participating research site (or their choice of site)
f) Notify the relevant site and request a baseline appointment booking (site are responsible for informing the patient of their baseline appointment date/time, i.e. verbally, appointment card, SMS text, email or letter)
g) Patients will be directed to view the main PIS on the trial website so they have time to read through ahead of their baseline appointment

4.7.3 Pre-baseline check criteria

The pre-baseline check will check that patients meet the minimum trial entry criteria:

a) Confirmation of COPD status
b) 35+ years old
c) Currently daily smoking
d) Motivated to stop smoking
e) Not currently taking part in another trial of COPD treatment/ management or smoking cessation
f) Check if patients have had an COPD exacerbation or inpatient hospital stay within the last 8 weeks and/or Contraindications to spirometry within the last 12 weeks

For criteria g, if a patient answers yes to any of these the baseline visit will be made when enough time has passed for them to be eligible (see exclusion criteria, section 6.2).

Where a patient is found to be unsuitable for a baseline visit as they have not met criteria a-f, their database record will be archived to be no longer accessible by the trial team and if applicable, their paper reply slip will be confidentially destroyed.

5. INFORMED CONSENT

Informed consent will be taken at the beginning of the baseline visit. It is the responsibility of the Principal Investigator (PI), or a suitably trained delegate, to obtain informed consent for each patient prior to performing any trial related procedures. This task can be delegated by the PI to other suitably trained members of the local research team, if local practice allows and this responsibility has been documented in the site signature and delegation log. Consent will be taken face to face on a paper consent form at research sites.

A Participant Information Sheet (PIS) will be provided when the patient is invited to take part in the trial, which will give them sufficient time to read it and discuss their participation with others outside of the site research team prior to consent. The PI, or delegate, will ensure that they adequately explain the aim of the trial, the trial intervention, and the anticipated benefits and potential hazards of taking part in the trial to the patient. They will also explain that participation is voluntary and that the patient is free to decide to take part and may withdraw from the trial at any time.

The patient will be given the opportunity to ask questions before signing and dating the current approved version of the Informed Consent Form (ICF). The PI or delegate will then sign and date the ICF. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes and the original placed in the Investigator Site File (ISF). Once the patient is randomised into the trial, the participant's trial number will be entered on the ICF maintained in the ISF. As part of the consent process, the patient is asked to give their permission for a copy of the signed ICF to be transferred to the trial team at BCTU for review.

Details of the informed consent discussions will be recorded in the patient's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant, version number of ICF signed and date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

At each visit the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Throughout the trial the participant will have the opportunity to ask questions about the trial. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue they will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

Electronic copies of the PIS and ICF will be available from the Trial Office and will be printed or photocopied onto the headed paper of the local institution.

6. INCLUSION/EXCLUSION CRITERIA

At the baseline visit, all potentially eligible patients will have their eligibility assessed against the following criteria:

6.1 Inclusion criteria

1. COPD diagnosis confirmed by post-bronchodilator spirometry (FEV_1/FVC <0.7), any GOLD stage
2. Current daily smoker
3. Willing to try to stop smoking using only allocated trial products
4. Aged 35 or over

6.2 Exclusion criteria

1. Unable to perform spirometry to a satisfactory standard (e.g. due to dementia, lack of teeth, lack of coordination or not having a good oral seal)
2. Deemed as unsuitable to participate in the trial (e.g. terminal illness, unable to give informed consent)
3. Unable to participate in behaviour support calls
4. Severe angina or unstable cardiovascular disease (CVD)
5. History of end stage kidney disease
6. History of cirrhosis of the liver
7. Currently taking part in another trial of smoking cessation or COPD treatment/ management
8. Contraindications to spirometry within the last 12 weeks – tuberculosis infection, cardiac infarction, retinal detachment, Pneumothorax or surgery on the chest, abdomen, brain, ears or eyes *(invite back and re-assess after 12 weeks)*

This will be undertaken by an appropriate member of site staff, delegated this responsibility on the ECAL Site Signature and Delegation Log. In some circumstances it is appropriate to have someone other than a qualified medical doctor assess eligibility. We have conducted a risk assessment and as the safety profile of the IMP is established as low risk and patients will not be put at any higher risk of side effects from either intervention than standard care, and the inclusion and exclusion criteria are straightforward, it is appropriate that eligibility can be delegated to an appropriately trained member of site staff overseen by a medically qualified doctor. Prior to randomisation, the eligibility of each trial participants will be confirmed by a delegated and suitably trained medically qualified doctor at site; confirmation of eligibility will be documented on the baseline assessment visit CRF prior to randomisation.

Details of all patients screened for trial will be recorded on the ECAL Participant Screening/Enrolment Log which will be kept in the ISF and should be available to be sent to the Trials Office upon request.

6.3 Co-enrolment

Potentially eligible patients who are already taking part in another trial for the treatment/management for COPD or smoking cessation will be excluded (this is an exclusion criteria). Similarly, ECAL participants will be made aware that they are not allowed to take part in any other trials for the treatment/management for COPD or smoking cessation.

The Trial Management Group (TMG) will consider requests for co-enrolment into other trials not related to COPD or smoking cessation in accordance with best practice recommendations. This will ensure careful consideration of patient burden, compatibility of interventions, organisational issues and follow-up.

7. RANDOMISATION and BLINDING

7.1 Randomisation process

After informed consent has been received, eligibility has been confirmed, and baseline assessments have been completed, the participant can be randomised into the trial using the REDCap trial database (see section 10.3 for baseline procedures).

Randomisation will be provided via the trial database using a secure online system (available at https://bctu-redcap.bham.ac.uk), thereby ensuring allocation concealment. Unique log-in usernames and passwords will be provided to those who wish to use the online system and who

have been delegated the role of randomising participants into the trial as detailed on the ECAL Site Signature and Delegation Log. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access either system using another person's login details. The online system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance which sites will be informed of in advance.

In the event of the online system not being available, a back-up telephone toll-free randomisation service (0800 953 0274) is available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays, government guided closures and University of Birmingham closed days.

Participants will be randomised at the level of the individual in a 1:1 ratio to either the intervention (EC) or comparator (NRT). A minimisation algorithm will be used within the online randomisation system to ensure balance in the treatment allocation over the following key potential confounding variables:

- COPD stage (levels: stage 1-2 and stage 3- 4 based on FEV_1)
- Age (levels: 35-65, 66+ years)
- Sex at birth (levels: male, female)
- Fagerstrom test for nicotine dependence (FTND) score (levels: ≤6, 7+)

To avoid the possibility of the intervention allocation becoming predictable, a random element will be included in the algorithm. Full details of the randomisation specification will be stored in a confidential document at BCTU.

Participants randomised by error, i.e. randomised twice or found ineligible according to inclusion/exclusion criteria after randomisation, will be replaced to attain the full sample size.

Following randomisation, a confirmatory e-mail will be sent to the local PI, research nurse/delegated person who randomised the participant. The trial team will also receive a randomisation confirmatory e-mail.

The local research team should add the participant to the ECAL Participant Recruitment and Identification Log which links patients with their Trial Number. PIs must maintain this document securely and it must not be submitted to the Trial Office. The ECAL Participant Recruitment and Identification Log should be held in strict confidence.

7.2 Blinding

This is an open-label trial and trial participants, care providers, investigators and outcome assessors will not be blinded to treatment allocation. This is because it is not possible to blind given the physical nature of the interventions. However, the primary outcome measure is validated using an objective measure (exhaled CO).

7.3 Informing the participant's GP and other parties

Patients will give explicit consent for their General Practitioner (GP) to be notified of their participation in the trial.

The participant's GP will be notified using the ECAL GP notification letter/ email, which will be sent directly from the randomising site. The GP notification letter/ email will include the name of the trial, the participant's randomised intervention allocation and also advise the GP to monitor their patient whilst they try to quit smoking.

As part of the trial risk protocol, the GP of participants who are identified as at risk (i.e., a HADS scoring of ≥11 and/or disclosure of other mental health related issues of concern) may need to be informed of this by letter/ email.

No other parties outside of the trial team will be informed of the participant's entry into the trial.

8. TRIAL INTERVENTION

8.1 Trial interventions and dosing schedule

Intervention arm: Electronic Cigarettes (EC) - Participants will receive an EC starter pack and an initial supply of e-liquid to start using the e-cigarette (up to 20 mg nicotine/ml). Participants will be advised on how to continue sourcing further supplies themselves from reputable vendors in their preferred nicotine strength and flavours. Participants in the intervention arm will be offered weekly telephone behavioural support up to 4 weeks post quit.

Comparator arm: Combination Nicotine Replacement Therapy (NRT) - Participants will receive up to 12-week supply of a nicotine patch plus a fast-acting nicotine product to be used in combination. A pragmatic approach to product allocation will allow for variation based on participant preference and availability. Participants who do not wish to use patches (e.g. due to previous experience of skin irritation) will be offered two types of fast acting product. Participants in the comparator arm will also be offered weekly telephone behavioural support up to 4 weeks post quit.

8.1.1 Telephone behavioural support

All participants will be advised at the baseline visit that they will receive six weekly behavioural support telephone calls from stop smoking advisors which will commence within a few days of the baseline visit. These will be delivered by the Health and Lifestyle Research Unit at the Wolfson Institute of Population Health at Queen Mary University of London (QMUL). During these calls, the advisor will deliver behavioural support according to the National Centre for Smoking Cessation Training Standard Programme[44] including setting a TQD and providing further support around medication use. The TQD will be set for approximately 2 weeks after the baseline visit. Should participants have already started their quit attempt at the first phone call, the -1 week and TQD behavioural support phone calls will be combined. If participants are unable to be contacted to set a TQD then a default TQD will be set (approximately 2 weeks after the baseline visit) for follow up time points to be based on.

8.2 Drug interaction or contraindications

8.2.1 Permitted medications/interventions (including rescue medication)

There are no known contraindications for NRT or ECs and no clinically relevant interactions between NRT and other drugs. For cautions see British National Formulary (BNF)/Summary of Product characteristics (SmPC).

8.2.2 Concomitant medications/interventions

Concomitant medications will be continued as per the participant's usual care plan.

8.2.3 Prohibited medication(s)/intervention(s)

There are no prohibited medications for participants whilst they are participating in this trial.

8.3 Intervention modification or discontinuation

In the main PIS, at the baseline visit and/or during the behavioural support phone calls, participants will be informed about potential side effects of combination NRT use and about

different e-liquid nicotine strength. Should participants experience side effects, they will be advised during behavioural support telephone calls to reduce their dose of nicotine/day.

If participants decide to discontinue use of combination NRT or ECs, this will be captured during the behavioural support telephone call and documented on a CRF. Discontinuation of use will not mean the participant has withdrawn (see section 10.11). Participants who want to continue with their quit attempt using a product not allocated to them as part of the trial will be advised to contact their local stop smoking service.

8.4 Continuation of intervention after the trial

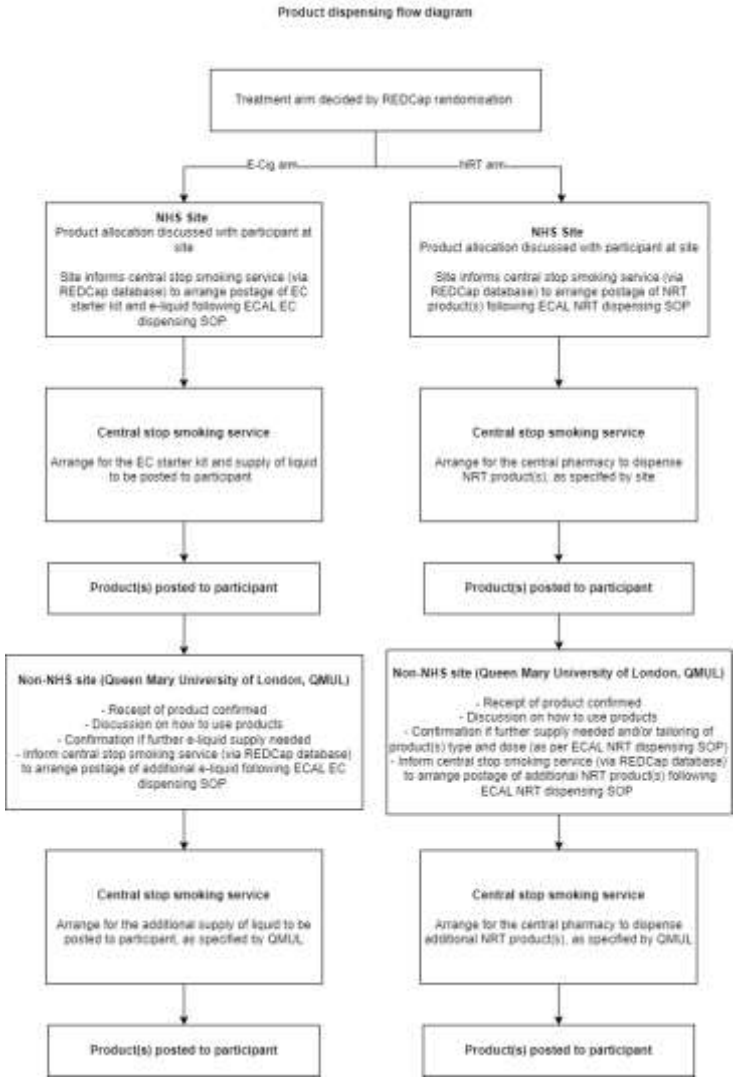
No further EC refills or NRT will be provided after participation in the trial has ended. Any continuation of ECs or NRT will be at the participant's expense and is not required for the trial.

8.5 Intervention supply and storage

8.5.1 Intervention supplies

All NRT products used within the trial will be classed as General Sales List medicines and will be used within their Marketing Authorisation (MA). The risk assessment has determined that there is no requirement for a prescription as these products are available to purchase from any shop without any supervision from a pharmacist or healthcare professional. Participants will indicate their choice of product(s) to be ordered, at the baseline visit (after randomisation) and during the behavioural support telephone calls (for any further supplies ordered). Allocated product orders will be sent to the central stop smoking service who will coordinate these being dispensed by a central pharmacy to participants through the post. At a minimum, sites should order an amount of NRT at the baseline visit to allow participants to start their quit attempt, and further supplies up of to 12 weeks will be made available to participant as identified at the behavioural support telephone calls. Product dispensing will depend on participants' choice and availability.

Note: The e-cigarette (EC) is not an Investigational Medicinal Product (IMP) in this trial as it is a consumer product regulated under the Tobacco and Related Product Regulations. The trial team will work with the central stop smoking service to coordinate the distribution of an EC starter pack to participants, but participants will be permitted to purchase a different EC device and/or e-liquid if the one provided does not work for them. E-cigarette start packs and e-liquid will be supplied from reputable vendors.



8.5.2 Packaging and labelling

There are no special packaging requirements for the IMP (NRT products) being used in the comparator arm, as this is an open-label RCT. Drug accountability and trial specific labelling will not be required due to Regulation 46 exemption.

There are no special labelling requirements for the EC starter kits as these are consumer products and this is an open label RCT.

8.5.3 NRT storage

NRT stock will be stored within the central pharmacy in line with product data sheets. Products will be supplied to participants as per the central pharmacy's SOPs.

8.5.4 Storage deviations

The IMP (NRT products) can normally be purchased over the counter. The central pharmacy will store products in accordance with product data sheets. Any storage deviations will be handled in line with the central pharmacy's policies.

8.5.5 IMP recalls

In the event that a trial product is recalled by the manufacturer, the central pharmacy who dispensed the products will be responsible. The central pharmacy will follow local their recall SOP and participants should be advised to contact the manufacturer if required.

8.6 Accountability

Drug accountability to allow traceability will be according to the central pharmacy's supply SOP. Participants will also be asked to self-report trial product use at the behavioural support telephone calls (1-, 2-, 3- and 4-weeks post TQD), at the 26 weeks follow up phone call and at the 52 week follow up visit.

8.7 Adherence

Adherence to trial products will be monitored through the behavioural support calls and at follow time points. All participants will be asked to self-report their use of allocated products.

9. OUTCOME MEASURES

N.B. all follow up points referred to in outcome measures for main trial, economic analysis and sub studies are calculated from the target quit day.

9.1 Internal pilot outcomes

The outcome of the internal pilot is progression to full trial (yes, no), and if yes, are any changes required. Decisions will be made based on pre-defined STOP-GO criteria (table 2 - traffic light criteria). The STOP-GO criteria will be assessed at 5 months post-start of recruitment.

Table 2 – Traffic light criteria

Green	Number of participants recruited: ≥100%
	Number of sites actively recruiting: 15
	Withdrawal from the trial due to unacceptability of ECs: <20%

If all three criteria are met; continue the trial with protocol unchanged (unless there is clear indication from our experience that would improve the protocol).

Amber	Number of participants recruited: 51-99%
	Number of sites actively recruiting: 7-14
	Withdrawal from the trial due to unacceptability of ECs: 20-49%

If one or more of the amber criteria are met, then the trial will need review to see what changes (if any) could be made to improve whichever criteria are not at the 'green' level before proceeding to the full trial.

Red	Number of participants recruited: ≤50%
	Number of sites actively recruiting: <7
	Withdrawal from the trial due to unacceptability of ECs: ≥50%

If one or more of the red criteria are met, we will discuss with the Trial Steering Committee (TSC) and the funder regarding feasibility of the trial continuing and contingency plans.

The definitions of the factors used in the stop-go criteria are:

- **Participants recruited:** The participants recruited will be calculated as a percentage. This will be the number of participants recruited in month 4 and 5 divided by the number of expected based on the number of open sites in month 4 and 5.
  For example, if we are successful in opening 20 sites during the pilot phase by month 4 as we are planning, we expect to recruit 160 participants during months 4 and 5 (Target monthly recruiting target = 4 patients/month/research site).
- **Number of sites actively recruiting:** An actively recruiting site is one that has been trained and is open to recruitment.
- **Complete withdrawal due to unacceptability of ECs:** Participants who ask to withdraw from the trial because being randomised to ECs is not acceptable.

At the end of the pilot phase, the TMG will prepare a report on trial progress for the independent TSC. There will also be an assessment of safety by the Data Monitoring Committee (DMC). Based on the traffic light criteria above and confirmation from the DMC that there are no safety issues to prevent the trial from continuing, the TSC will recommend if the RCT should continue or not.

9.2 Main trial outcomes

9.2.1 Primary outcome

Abstinence from smoking since TQD biochemically validated (exhaled CO<8ppm) at 52 weeks post TQD, defined in accordance with the Russell Standard[1]

9.2.2 Secondary outcomes

1. Abstinence from smoking for at least 26 weeks biochemically validated (exhaled CO<8ppm) at 52 weeks

2. 7-day point prevalence abstinence from smoking biochemically validated (exhaled CO<8ppm) at 52 weeks

3. Self-reported abstinence from smoking for at least 26 weeks at 52 weeks

4. Self-reported 7-day point prevalence abstinence from smoking at 4, 26 and 52 weeks

5. Reduction in cigarettes smoked (self-report of any and > 50% reduction from baseline to 52 weeks, confirmed by reductions in expired CO readings at 52 weeks)

6. Reduction in cigarettes smoked (self-report of any and > 50% reduction from baseline to 26/52 weeks)

7. Continued use of allocated product at 4, 26 and 52 weeks

8. Withdrawal symptoms and urges to smoke (change from baseline to 1/ 2/ 3/ 4 weeks) measured using the mood and physical symptom scale (MPSS)

9. COPD Symptoms (change from baseline to 4/ 26/ 52 weeks) measured using COPD Assessment Test (CAT) and the Clinical COPD Questionnaire (CCQ)

10. Number of COPD exacerbations over the past 52 weeks (from baseline to 52 weeks)

11. Number of self-reported upper respiratory tract infections over the past 52 weeks (from baseline to 52 weeks)

12. Post bronchodilator spirometry (FEV_1, FVC and MMEF change from baseline to 52 weeks)
    - Forced Expiratory Volume in 1 Second (FEV1): The maximal volume of air that can be expired in the first second of a forced expiration from a position of full inspiration (measured in Litres (L) and also expressed as the % predicted for age, sex, height and race)
    - Forced Vital Capacity (FVC): The maximal volume of air that can be expired during a forced and complete expiration from a position of full inspiration (measured in L and % predicted)
    - Mean Mid-Expiratory Flow (MMEF): The average flow between 25% and 75% of the FVC manoeuvre (measured in L/sec and % predicted)

9.3 Health economic outcomes

1. Health-related quality of life (EQ-5D-5L) (change from baseline to 4/ 26/ 52 weeks)

2. Use of healthcare resources and costs (measured at 26 and 52 weeks)

3. Cost-effectiveness based on cost per quitter and cost per Quality-Adjusted Life-Year (QALY) at 52 weeks, and modelled cost per QALY over patient lifetime

9.4 Lung health sub-study outcomes (subset of participants included in the cohort analysis only):

1. COPD Symptoms (change from baseline to 4/ 26/ 52 weeks) measured using COPD Assessment Test (CAT) and the Clinical COPD Questionnaire (CCQ)

2. Health-related quality of life (EQ-5D-5L) (change from baseline to 4/ 26/ 52 weeks)

3. Number of COPD exacerbations over the past 52 weeks (from baseline to 52 weeks)

4. Self-reported upper respiratory tract infections over the past 52 weeks (change from baseline to 52 weeks)

5. Post bronchodilator spirometry (FEV_1, FVC and MMEF change from baseline to 52 weeks)
   - Forced Expiratory Volume in 1 Second (FEV_1)*:* The maximal volume of air that can be expired in the first second of a forced expiration from a position of full inspiration (measured in Litres (L) and also expressed as the % predicted for age, sex, height and race)
   - Forced Vital Capacity (FVC): The maximal volume of air that can be expired during a forced and complete expiration from a position of full inspiration (measured in L and % predicted)
   - Mean Mid-Expiratory Flow (MMEF): The average flow between 25% and 75% of the FVC manoeuvre (measured in L/sec and % predicted)

6. Full blood count (total and differential white blood cell (WBC) count $x10^9$/L) (change from baseline to 52 weeks)

7. Serum/plasma biomarkers such as but not restricted to cytokines such as IL-6, IL-8, TNF-α; antimicrobial peptides; and markers of proteinase activity (change from baseline to 52 weeks)

8. Toxicant analysis; to include toxicants such as formaldehyde, acetaldehyde, acrolein (change from baseline to 52 weeks)

9.5 Wellbeing sub-study outcomes (subset of participants included in the cohort analysis only):

1. Anxiety - Hospital Anxiety and Depression Scale (HADS) (change from baseline to 52 weeks)

2. Depression - HADS (change from baseline to 52 weeks)

3. Mixed anxiety and depression - EQ-5D-5L (change from baseline to 52 weeks)

4. Breathing related depression and social quality of life - CCQ (change from baseline to 52 weeks)

10. TRIAL PROCEDURES

10.1 Patient identification and invitation to participate

Potentially eligible patients will be identified and invited to take part in the trial (section 4).

10.2 Pre-baseline check

Patients who are interested in taking part in the trial will need to undergo a trial pre-baseline check (section 4.5). The pre-baseline check is conducted by a delegated member of site staff, BCTU trial office or QMUL trial team. If a patient fulfils the initial pre-baseline criteria (section 4.5.1), a baseline visit will be arranged to take place at the patient's local participating research site. This appointment must take place at least 12 weeks after any contraindication to spirometry. Once the baseline visit date/time is confirmed, the patient will be notified, i.e. verbally, appointment card, SMS text, email or letter.

10.3 Baseline visit

The baseline visit will occur face-to-face at a participating research site. At the start of the baseline visit, patients will have an opportunity to ask questions about the trial before being asked to provide full informed consent (section 5). Once consent is obtained, the patient will be screened against inclusion and exclusion criteria (section 6), which includes post bronchodilator

spirometry to check FEV1/FVC < 0.7 and to collect FEV1, FVC and MMEF values for outcome assessment. Site staff will complete the baseline CRF with participants, and participants will complete the baseline participant questionnaire, give an exhaled CO reading (section 10.9) and provide a blood sample (section 10.10). If a patient meets the eligibility criteria, as confirmed by a medically qualified doctor, and once all baseline measures have been collected, the patient will then be randomised into the trial (section 7). The research nurse will inform the participant of their randomised treatment allocation. Allocated products will be coordinated by a central stop smoking service as described in section 8. Participants will be given a £15 voucher to thank them for their time and will be reimbursed for their travel, and car parking as necessary.

10.4 Behavioural support telephone calls -1w, TQD, +1w, +2w, +3w, +4w

Shortly after the baseline visit, participants will be contacted by telephone by the research team from the Health and Lifestyle Research Unit at the Wolfson Institute of Population Health at QMUL. During this call, the stop smoking advisor will deliver behavioural support following the standard treatment programme from the National Centre for Smoking Cessation Training.[57] Data collected during these calls, including all adverse events, will be recorded on specially designed CRFs. At the baseline visit, participants will be advised not to start their quit attempt until after the first behavioural support phone call (-1 week). However, if at the -1 week behavioural support telephone call, a participant has already started their quit attempt, the -1 week and TDQ phone call will be combined.

If a participant is unable to be contacted after 3 attempts, the QMUL trial team will send a letter/ email/ SMS text message. The participant will be asked to make contact with the QMUL team as soon as possible to collect the data for this time point. If no contact is established within 3 days of the call due date, this data will be considered missing for this follow up time point.

10.5 4-week follow up

In addition to the behavioural support offered at 4 weeks, a follow up questionnaire will be completed during the phone call carried out by the QMUL trial team. If a participant is unable to be contacted after 3 attempts, the QMUL trial team will send a 4-week minimum data collection (MDC) questionnaire, by post (paper) and/or email (with online link), to the participant. The participant will be asked to complete and return the questionnaire to the trial team at BCTU, in the format it was received. If no response is received within 14 days of follow up due date, this data will be considered missing for this follow up time point.

10.6 26-week follow up

The 26 week follow up call will be carried out by the Health and Lifestyle Research Unit, Wolfson Institute of Population Health, QMUL over the phone. During this call, the trial team will complete the 26-week CRF and follow up questionnaire with participants. If a participant is unable to be contacted after 3 attempts, the trial team will send the 26-week minimum data collection (MDC) questionnaire, by post (paper) and/or email (with online link), to the participant. The participant will be asked to complete and return the questionnaire to the trial team at BCTU, in the format it was received. If no response is received within 30 days of follow up due date, this data will be considered missing for this follow up time point.

10.7 52-week follow up

Participants will be contacted by the research site or trial team member to set up the 52 week follow up visit which will take place at the research site. This appointment must take place at least 12 weeks after any contraindication to spirometry. Once the follow-up visit date/time is confirmed, the patient will be notified, i.e. verbally, appointment card, SMS text, email or letter. At the 52-week visit, site staff will complete the 52-week CRF with participants, and participants

will complete a participant questionnaire, undergo spirometry to give FEV1, FVC and MMEF readings (section 10.8), give an exhaled CO reading (section 10.9) and provide a blood sample (section 10.10). Participants will be given a £15 voucher to thank them for their time and will be reimbursed for their travel, and car parking as necessary.

If a participant is unable to be contacted to arrange a 52-week follow up visit after 3 attempts, the trial team will send a letter or email to the participant. This letter/ email will remind the participant that their 52-week follow up is due and ask them to contact the trial office to arrange their follow-up visit.

If the participant makes no contact, after approximately 14 days of last contact attempt, the trial team will send a 52-week minimum data collection (MDC) questionnaire out to the participant. This will be sent either by post (paper) or email (with online link). The participant will be asked to complete and return the questionnaire to the trial team at BCTU, in the format it was received. If no response is received within 100 days of the 52-week follow up due date, this participant will be considered lost to follow-up and the data will be considered missing for this follow up time point.

10.8 Spirometry

Participants will be asked to undergo a spirometric assessment at the baseline visit and at the 52 week follow up visit. Post-bronchodilator spirometry will be undertaken according to ATS/ERS 2019 guidelines[58] and carried out by practitioners trained to ARTP or ERS Standard. FEV1, FVC and MMEF will be measured using a verified/calibrated spirometer.

A pragmatic approach will allow sites to use the spirometry equipment available. To minimise the variability, all sites will be asked to use lab/desktop spirometers and if possible, use the same equipment at the baseline and the 52-week follow up visits. Details of the spirometry equipment make, model and date last calibrated/ verified will be recorded on the relevant CRFs.

It is also anticipated that there could be between-technician variability. Spirometry will be undertaken by trained site staff, some of whom undertake this as part of usual care. The trial team will ask sites to delegate lung function testing to ARTP certified staff. If this is not feasible, the trial team will provide spirometry training modelled on the ARTP standard. This training will be provided by an experienced professional. During this training those trained will have their spirometry outputs checked to ensure they achieve the correct level of competence before being delegated this role for the trial. During the trial, quality checks will also be performed on a sample of spirometry results from each participating site.

10.9 Exhaled CO measurement

Participants will be asked to undergo assessment of exhaled CO levels at the baseline visit and at the 52 week follow up visit. Exhaled CO will be measured using a CO monitor and recorded as parts per million (ppm).

10.10 Collection and management of blood samples

Ideally between 36-45ml of blood will be collected from each participant at baseline and again at the 52 weeks follow up visit at the research sites. One EDTA tube will be used to conduct full blood following standard protocols. The remaining blood will be centrifuged for plasma/serum collection and storage. Samples will be maintained at -80 ^{o}C at the research sites. Sites unable to maintain samples at -80 ^{o}C may hold samples temporarily at -20 ^{o}C before shipping to the primary site (University of Birmingham Research Laboratories, Queen Elizabeth Hospital, Birmingham (QEHB)). Samples will be shipped to the primary site as capacity and storage conditions demands.

All samples will be shipped in a temperature-controlled environment on dry ice. Blood samples from participants who self-report quitting smoking and not vaping (quitters) or switching to exclusive e-cigarette use (vaping) will be sent to a contracted external laboratory to test cotinine levels. For participants who meet the inclusion criteria for the cohort analysis (based on smoking and vaping status) blood will be analysed for biomarkers and toxicants at the University of Birmingham or will be transported to contracted external laboratories for analysis.

Table 3: Schedule of Assessments

Visit	*Identification of participants/ Pre-baseline assessment*	*Baseline*	*-1w pre TDQ*	*Target Quit day (TQD) + 3 days*	*+1 week post TQD ± 3 days*	*+2 week post TQD ± 3 days*	*+3 week post TQD ± 3 days*	*+4 week post TQD ± 14 days*	*26 week post TQD + 30 days*	*52 week post TQD + 100 days*
Eligibility check	*x*	*x*								
Valid informed consent		*x*								
Concomitant medication check		*x*								
Relevant medical history taken		*x*								
Randomisation		*x*								
Dispensing of IMP (EC or Combination NRT)		*x*								
Behavioural support			*x*	*x*	*x*	*x*	*x*	*x*		
Instructions to patient about the trial		*x*								
Blood sample		*x*								*x*
Spirometry		*x*								*x*
Exhaled CO measurement		*x*								*x*
*Baseline questionnaire**		*x*								
*Behavioural support session questionnaire***								*x*		*x*
*Follow up questionnaire****									*x*	*x*

**Baseline questionnaire includes the following validated questionnaires:* COPD assessment test (CAT), *Hospital anxiety and Depression Scale (HADS), Clinical COPD Questionnaire (CCQ) for measuring COPD symptoms., EQ-5D-5L for measuring quality of life for the economic evaluation., Fagerstrom Test for Nicotine Dependence (FTND).*

***Behavioural support session questionnaire (at 4 weeks) includes the following questionnaires: Mood and physical symptom score (MPSS) for measuring nicotine withdrawal symptoms,* COPD assessment test (CAT), *Clinical COPD Questionnaire (CCQ) for measuring COPD symptoms and EQ-5D-5L† for measuring quality of life for the economic evaluation.*

****Follow up questionnaire includes the following validated questionnaires:* COPD assessment test (CAT) – 26w and 52w, *Clinical COPD Questionnaire (CCQ) for measuring COPD symptoms - 26w and 52w, EQ-5D-5L for measuring quality of life for the economic evaluation – 26w and 52w, and Hospital anxiety and Depression Scale (HADS) – 52w only .*

† Validated for delivery over the telephone

10.11 Withdrawal and changes in level of participation

Participants will be able to withdraw from the trial at any time. This will not put at risk their usual medical care for COPD. Failure to be contacted as part of the trial will not count as withdrawal from the trial. The only trial withdrawals will be the following:

- **No behavioural support calls:** The participant would no longer like to receive the behavioural support calls but is willing to be followed up in accordance with the schedule of assessments (i.e., the participant has agreed that data can continue to be collected and used in the trial analysis).

- **No further data collection:** The participant is not willing to be followed up in any way for the purposes of the trial AND does not wish for any further data to be collected (i.e., only data collected prior to any changes of levels in participation can be used in the trial analysis).

Participants are free to stop using the allocated intervention (ECs or NRT) at any time; the participant will not be withdrawn in these circumstance. In the event of a Serious Adverse Event (SAE) or Suspect Unexpected Serious Adverse Reaction (SUSAR) that is judged to be related to NRT or EC, the Chief Investigator (CI) will review the case and if deemed appropriate, the participant will be advised to stop using the medication.

The details of withdrawal should be clearly documented in a withdrawal form. Participants will be asked their reason for withdrawal, but it will be made clear that they are not obliged to give a reason.

In any case of withdrawal, participants will be offered standard care for smoking cessation as per local site protocol for COPD. Additionally, if a participant dies or is lost to follow-up during their participation in the trial, this should also be documented in the source documents and the trial team at BCTU should be notified.

The Trial Office will inform the research sites and QMUL if they are informed by a participant that they wish to withdraw from the trial and vice versa.

11. ADVERSE EVENT REPORTING

11.1 Definitions

Table 4: Adverse event reporting definitions

Severity Definitions	Mild Moderate Severe	Awareness of signs or symptoms that do not interfere with the participant's usual activity or are transient and resolved without treatment and with no sequelae. A sign or symptom, which interferes with the participant's usual activity. Incapacity with inability to do work or perform usual activities.
Adverse Event	AE	Any untoward medical occurrence in a participant administered a medicinal product and which does not necessarily have a causal relationship with this intervention. Comment: An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.
Adverse Reaction	AR	All untoward and unintended responses to an IMP related to any dose administered. Comment: An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.
Serious Adverse Event	SAE	Any untoward medical occurrence or effect that: Results in death Is life-threatening* Requires hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability or incapacity Is a congenital anomaly/birth defect Or is otherwise considered medically significant by the Investigator**
Serious Adverse Reaction	SAR	An AR which also meets the definition of a SAE.

Unexpected Adverse Reaction	UAR	An AR, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SmPC) for a licensed product). When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
Suspected Unexpected Serious Adverse Reaction	SUSAR	A SAR that is unexpected i.e., the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR.

* The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.
** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definitions above.

11.2 Adverse event recording – general

The recording and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care Research, the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments) and the requirements of the Health Research Authority (HRA) and the Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments thereof. Definitions for adverse event reporting are listed in Table 4: Adverse event reporting definitions in Section 11.1.

It is routine practice to record AEs in the participant's medical notes and it is also recommended that this includes the documentation of the assessment of severity and seriousness and of causality (relatedness) in relation to the intervention(s) in accordance with the protocol.

11.3 Adverse event reporting in the ECAL trial

The reporting period for AEs will be from randomisation until 26 weeks after agreed target quit day/ default target quit day. By this time point the trial supply of intervention product will have ended.

The safety profile for this trial population and interventions are well characterised so although the severity and causality of all AEs should be recorded in the patient's medical notes, a strategy of targeted reporting (to the sponsor) of AEs will not affect the safety of participants. Only the following AEs will be reported via the CRF completed during the scheduled follow up appointments and behavioural support calls:

- Rash/local skin irritation
- Nausea/vomiting
- Throat/mouth irritation
- Sleep disturbances
- Dizziness
- Headache
- Constipation

- Diarrhoea

11.4 Serious Adverse Event (SAE) reporting in ECAL trial

All adverse events which meet the definition of serious must be recorded in the participant medical notes, including the causality and severity. The reporting period for SAEs will be from randomisation until 26 weeks after agreed set target quit day/ default target quit day. When an SAE is identified during a scheduled telephone call with a participant, the trial team will notify the research site to investigate.

For all SAEs, the PI or delegate must do one of the following:

1. **Record safety reporting-exempt SAEs** in the medical notes but **not report** them to the trials office on an SAE form as per Section 11.4.1 Serious Adverse Events not requiring reporting to the Trial Office.

2. **Report SAEs to the trial office in a non-expedited manner**. This can only be done for the pre-defined subset of SAEs as per Section 11.4.2 Serious Adverse Events requiring non-expedited reporting to the Trial Office.

3. **Report SAEs to the trial office in an expedited manner** (within 24 hours of the site research team becoming aware of the event). All SAEs not covered by the above 2 categories must be reported as per Section 11.4.3 SAE Reporting process.

Note: when an SAE occurs at the same site at which the participant is receiving a trial product or is being followed up for trial purposes, processes must be in place to make the trial team at the site aware of any SAEs, regardless of which department first becomes aware of the event, in an expedited manner.

In addition, any SAE reported to the trial team by the participant will be passed to the PI to ensure the SAE is noted in the participant's medical notes. Where the SAE requires causality assessment, we will follow up with the PI until resolution of the SAE.

11.4.1 Serious Adverse Events not requiring reporting to the Trial Office

Safety reporting exempt SAEs must be recorded in the participant medical notes, including the causality and severity, but for trial purposes these events do not require reporting on the SAE CRF. The following will be considered as safety reporting exempt SAEs:

1. Pre-planned elective hospitalisation for any reason
2. Congenital anomalies or birth defects in the offspring of participants

11.4.2 Serious Adverse Events requiring non-expedited reporting to the Trial Office

The population enrolling in ECAL are expected to be admitted for reasons related to COPD. In this case such an SAE is protocol-defined as "expected" (see Section 11.5.2 Assessment of expectedness of an SAE by the CI). The following will be considered as expected SAEs:

1. Admission for exacerbation of COPD
2. Community acquired pneumonia
3. Lung cancer events
4. Cardiovascular events

Such events should still be recorded by the trial team in the participant's medical notes and reported to the Trial Office on the trial outcome CRF, but it does not require expedited reporting (immediately on the site becoming aware of the event) since the assessment of expectedness for

the specified events has been pre-defined. They should be reported within 2 weeks of site being aware of the event.

11.4.3 Serious Adverse Events requiring expedited reporting to the Trial Office
All SAEs not listed in section 11.4.1 or section 11.4.2 must be reported to the Trial Office on a trial specific SAE CRF within 24 hours of the site research team becoming aware of the event.

11.5 SAE Reporting process
On becoming aware that a participant has experienced an SAE which requires expedited reporting on an SAE CRF, the PI or delegate should report the SAE to their own Trust in accordance with local practice and to the Trial Office.

To report an SAE to the Trial Office, the PI or delegate must complete, date and sign the trial specific CRF. The completed form together with any other relevant, appropriately anonymised, data should be submitted to the Trial Office using the information below within 24 hours.

To report an SAE, submit via the trial database

Where an SAE CRF has been completed by someone other than the PI initially, the SAE CRF form will be signed off by the PI to confirm agreement with the causality and severity assessments.

On receipt of an SAE CRF, the Trial Office will allocate each SAE a unique reference number and notify the site via email to the site as proof of receipt. The site and the Trial Office should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the ISF.

If the site has not received confirmation of receipt of the SAE or if the SAE has not been assigned a unique SAE identification number within 1 working day of reporting, the site should contact the Trial Office.

11.5.1 Assessment of causality of an SAE
When completing the SAE CRF, the PI (or, throughout this section, a medically qualified delegate) will be asked to define the nature of the seriousness and causality (Table 5: Categories of causality) of the event.

In defining the causality, the PI must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE CRF. It is not necessary to report concomitant events or medications which did not contribute to the event.

As per Table 5: Categories of causality, all events considered to be ‘possibly’, ‘probably’, or ‘definitely’ related to the intervention will be reported by the trial office as ‘related’; all events considered at site to be ‘unlikely’ or ‘unrelated’ to the intervention will be reported by the trials office as ‘unrelated’. The same categorisation should be used when describing AEs and protocol-exempt SAEs in the source data.

Table 5: Categories of causality

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g., the participant's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

11.5.2Assessment of expectedness of an SAE by the CI

On receipt of an SAE CRF, the Trial Office will forward it, with the unique reference number, to the Chief Investigator (CI) or delegate(s) who will independently* review the causality of the SAE. An SAE judged by the PI or CI or delegate(s) to have a reasonable causal relationship ("Related" as per Table 5: Categories of causality) with the intervention will be regarded as a related SAE (i.e., SAR). The severity and causality assessment given by the PI will not be downgraded by the CI or delegate(s). If the CI or delegate(s) disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

*Where the CI is also the reporting PI an independent clinical causality review will be performed.

The CI or delegate(s) will also assess all related SAEs for expectedness with reference to the criteria in table 6.

Table 6: Categories of expectedness

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures or that is clearly defined in the reference safety information (RSI).
Unexpected	An adverse event that is not consistent with known information about the trial related procedures and/or is not clearly defined in the RSI.

The most recently published Summary of Product Characteristics (SmPC) found on the Electronic Medicines Compendium (emc) for 25mg Transdermal Patches with reference to *Section 4.8 Undesirable effects* will be used for the purposes of the RSI. This is reflective of all NRTs. E-Cigarettes are a commercial product not a medical product. As such there is no requirement for safety profiling and no SmPC to inform the RSI. The most recently published SmPC for 15mg Inhalator will be used as a guide on which to base assessment of expectedness (as per MHRA guidance ref: Guidance for licensing electronic cigarettes and other inhaled nicotine-containing products as medicines - GOV.UK (www.gov.uk)).

The CI will undertake review of all SAEs and may request further information from the clinical team at site for any given event(s) to assist in this.

If the event is unexpected (i.e., it is not defined in the approved version of the RSI) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

11.5.3 Provision of SAE follow-up information

Following reporting of an SAE for a participant, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the Trial Office. Once the SAE has been resolved, all critical follow-up information has been received and the paperwork is complete, a copy of the final version of the completed SAE CRF must be submitted to the Trial Office and, if paper, the original kept in the ISF.

11.6 Reporting SAEs to third parties

The independent Data Monitoring Committee (DMC) may review any SAEs at their meetings.

The Trial Office will report details of all SARs (including SUSARs) to the MHRA, Research Ethics Committee (REC), and UoB Research Governance Team (RGT) annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR).

Additionally, the Trial Office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the MHRA, REC, and RGT within 7 days of being notified. Follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported within 15 days of being notified.

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to the PIs. A copy of any such correspondence should be filed in the ISF and Trial Master File (TMF).

SUSARs may be reported to the manufacturer of the Investigational Medicinal Product by the trial office within a reasonable timeframe.

11.7 Urgent Safety Measures

If any urgent safety measures are taken, the Trial Office shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC and MHRA of the measures taken and the reason why they have been taken.

11.8 Follow-up of pregnancy outcomes for potential SAEs

All trial participants will be current daily smokers at the start of the trial. Nicotine products have a lower risk to health generally and in pregnancy than that expected with smoking tobacco. NICE guidelines support the use of nicotine replacement products during pregnancy for smoking cessation as it is considered safer than cigarette smoking. Therefore, congenital anomalies or birth defects in the offspring of participants will not be reported as part of this trial.

12. DATA HANDLING AND RECORD KEEPING

12.1 Source data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of participants, source data will be accessible and maintained.

Table 7: Source data in ECAL trial

Data	Source
Patient reported data (questionnaires)	This may be paper or electronic. If completed on paper, the original participant-completed paper form is the source data. If completed directly into the REDCap database, this electronic record is the source.
Baseline, behavioural support call and Follow up data	Data is entered directly into the ECAL trial system which is the source data however details will also be kept in medical notes. It is held on BCTU severs on the REDCap data entry system. (If paper copies are used these will be the source).
Lab results (FBC, Toxicant analysis, biomarkers, cotinine)	The original records (which may be electronic) is the source data and will be kept and maintained, in line with normal local practice. Information will be transcribed onto CRFs.
Bronchodilator spirometry tests	The original records, which may be electronic records, are the source data. They will be kept and maintained in line with normal local practice. Information will be transcribed onto CRFs.
Clinical event data	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g. phone calls), must be documented in the source documents.
Trial-specific event data	The main trial CRF is the source for data that would otherwise not routinely be recorded in the patient's medical records.
Recruitment	The original record of the randomisation is the source. It is held on BCTU servers as part of the randomisation and data entry system.
Withdrawal	Where a participant expressed a wish to withdraw, the conversation must be recorded in the source data.

12.2 Case Report Form (CRF) completion

The CRFs will include (but will NOT be limited to) the following Forms (see table 8).

Table 8: Case report forms in the ECAL trial

CRF Name	Schedule for completion at site	Schedule for submission to BCTU
Consent to contact	Patient expression of interest in the trial (direct to site)	Immediately if entered onto study database, or if paper as soon as possible after consent to contact being given

CRF Name	Schedule for completion at site	Schedule for submission to BCTU
Pre-baseline check	Pre-baseline check prior to baseline appointment booking	Immediately if entered onto study database, or if paper as soon as possible after pre-baseline assessment
Informed Consent form	Baseline assessment visit	As soon as possible after baseline assessment visit
Baseline Assessment Visit	Baseline assessment visit	Immediately if entered onto study database, or if paper as soon as possible after the baseline assessment visit
Randomisation	Baseline assessment visit	Immediately if entered onto study database, or if paper as soon as possible after the participant has been randomised
Baseline Blood Results: Full Blood Count (FBC)	Upon receipt of baseline FBC blood results	as soon as possible after the Baseline assessment visit
Pre-quit day	- 1 week behavioural support call	Immediately if entered onto study database, or if paper as soon as possible after telephone behavioural support
Quit day call	Quit day behavioural support call	Immediately if entered onto study database, or if paper as soon as possible after telephone behavioural support
Weekly +1w, +2w, +3w Post Quit Day	+1 week, +2 week, +3 week behavioural support calls	Immediately if entered onto study database, or if paper as soon as possible after telephone behavioural support
Weekly +4w Post Quit Day	+4 week behavioural support call	Immediately if entered onto study database, or if paper as soon as possible after telephone behavioural support
26 week	26 week follow up call	Immediately if entered onto study database, or if paper as soon as possible after the Week 26 visit
52 week	52 week follow up visit	Immediately if entered onto study database, or if paper as soon as possible after the Week 52 visit
52 week Blood Results: Full Blood Count (FBC)	Upon receipt of 52 week FBC blood results	As soon as possible after the Week 52 visit
Serious Adverse Event Form	On becoming aware of an SAE	Immediately if entered onto study database, or if paper as soon as possible after, or if paper emailed to BCTU within 24 hours of research staff at site becoming aware of event
Withdrawal Form	On patient request	At the point of discontinuation or withdrawal

A CRF should be completed for each individual participant.

In all cases it remains the responsibility of the PI to ensure that the CRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the PI, or delegate(s). The Site Signature & Delegation Log will identify all those personnel with responsibilities for data collection.

The delegated staff completing the CRF should ensure the accuracy, completeness and timeliness of the data reported. This will be evidenced by signing and dating the CRF.

Data reported on each CRF will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained initially via a site initiation meeting or by other trained members at each site to adhere to procedures.

The following guidance applies to data and partial data:

- Only CRFs provided by the Trial Office should be used.
- Original completed CRFs or true copies should be sent to the Trial Office with copies filed in the ISF.
- Entries should be made in dark ink and must be legible.
- Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated.
- Time format – all times should be in accordance with the 24hr clock
- Rounding conventions – rounding should be to the nearest whole number: If the number you are rounding is followed by 5, 6, 7, 8, or 9, round the number up. **Example**: 3.8 rounded to the nearest whole number is 4. If the number you are rounding is followed by 1, 2, 3 or 4, round the number down. **Example**: 3.4 rounded to the nearest whole number is 3
- Trial-specific interpretation of data fields – where guidance is needed additional information will be supplied
- Entry requirements for concomitant medications (generic or brand names) – generic names should be used where possible
- Missing/incomplete data – should be clearly indicated – all blank fields will be queried by the Trial Office
- Repeat laboratory tests – the data used to inform clinical decisions should always be supplied. If a test is repeated it is either to confirm or clarify a previous reading. Confirmatory tests should use the original test values.
- Protocol and GCP non-compliances should be reported to the Trial Office on discovery.

On completion of paper CRFs, a copy or a scan of each form will be submitted to the Trial Office for entry into the database by the data manager and the original filed in the ISF. Electronic CRFs will be directly entered onto the REDCap trial database by a delegated member of site staff or trial team member.

12.3 Participant completed questionnaires

Participant completed questionnaires can be completed in clinic, during behavioural support calls or via postal paper questionnaires.

Participants will complete a questionnaire at baseline, +4 weeks behavioural support telephone call, 26 weeks and 52 weeks after TQD. The following validated questionnaires will also be used as an assessment of health and quality of life for patients with COPD:

- Mood and physical symptom score (MPSS) for measuring nicotine withdrawal symptoms.
- COPD assessment test (CAT).
- Hospital anxiety and Depression Scale (HADS)
- Clinical COPD Questionnaire (CCQ) for measuring COPD symptoms.
- EQ-5D-5L for measuring quality of life for the economic evaluation.
- Fagerström Test for Nicotine Dependence (FTND)

A bespoke resource use questionnaire developed from existing COPD resource use questionnaires will be completed at 26-week and 52-week for the economic evaluation.

Baseline and 52-week questionnaires will be completed on paper. Data collected on paper forms will then be transcribed onto the REDCap data capture system by a delegated member of site staff or the Trial Office. If for any reason a Baseline or 52-week questionnaire has not been completed during the clinic visit, an MDC questionnaire will be collected via post and transcribed into the REDCap database.

Participant questionnaires at +4 weeks behavioural support telephone call and 26 week follow up can be completed by telephone with the support of the smoking cessation advisor. If necessary, an MDC 4+ week or 26-week questionnaire will be sent via post to a participant for completion.

If completed in clinic, the questionnaire should be completed by the participant alone but physical assistance in completing the form can be given by site staff or the participant's friends and relatives where appropriate. In such circumstances, questions are to be read to the participant verbatim and the responses must not be led by the person assisting with the completion. This requirement should be made clear when the participant's friends and relatives are helping.

Participants should be encouraged to respond to all questions but can refuse to answer any, or all, of the questions should they wish. Where a questionnaire is returned to site staff, in person, with some questions unanswered, site staff should clarify with the participant that they have chosen not to respond specifically to the unanswered questions and that they have not simply missed them in error.

If completed via post, a paper questionnaire should be completed by the participant directly who will be asked to return it to the trial office in a pre-paid envelope. Upon receipt, a member of the trial team will check the completed questionnaire and can contact the participant by telephone, post, or email to query any missing data.

If completed on-line, an electronic version of the questionnaire will be completed by a member of the QMUL trial team under the direction of the participant. Upon submission, the Trial Office will check the completed questionnaire and can contact the participant by telephone, post or email to query any missing data.

If completed by remote video or telephone, the questionnaire will be completed by a member of the QMUL trial team under the direction of the participant. The questions are to be read to the participant verbatim and the responses must not be led by the trial team member conducting the remote video or telephone call. The participant will be encouraged to answer the questions as fully as they can.

12.4 Data management
Processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan and include the processes of data entry, data queries and self-evident corrections on trial data.

Where possible, trial data will be entered directly into the REDCap trial database, by a delegated member of site staff or the trial team, with the exception of paper reply slips and questionnaires. If online data collection is not possible for any reason, a paper version of the document will be completed and transcribed into the REDCap trial database by the site or Trial Office.

The REDCap data capture system will conduct automatic range checks for specific data values to ensure high levels of data quality. Queries will be raised via the REDCap trial database, with the expectation that these queries will be completed by the site within 30 days of receipt.

12.5 Self-evident corrections
The below self-evident corrections will be permitted on paper CRFs by the Trial Office:

- **Contingent fields:** When a response to a question determines, to a degree, the response required by a second question, then conflicts in the responses can be resolved by the data entry clerk e.g. Has the person had procedure "x"? If yes, state type. If the response to the first question is "no", yet the type of procedure is stated, it is self-evidently true that the initial response was incorrect.

12.6 Data security
UoB has policies in place which are designed to protect the security, accuracy, integrity and confidentiality of Personal Data. The trial will be registered with the Data Protection Officer at UoB and will hold data in accordance with the Data Protection Act (2018 and subsequent amendments). The Trial Office has arrangements in place for the secure storage and processing of the trial data which comply with UoB policies.

The Trial Database System incorporates the following security countermeasures:

Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.

Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate controls of non-identifiable data.

Network security measures: including site firewalls, antivirus software and separate secure network protected hosting.

System management: the system will be developed by the Programming Team at the Trial Office, and will be implemented and maintained by the Programming Team.

System design: the system will comprise of a database and a data entry application with firewalls, restricted access, encryption and role-based security controls.

Operational processes: the data will be processed and stored within BCTU (University of Birmingham).

System audit: The system will benefit from the following internal/external audit arrangements:

- Internal audit of the system
- Periodic IT risk assessment

Data Protection Registration: UoB's Data Protection Registration number is Z6195856.

12.7 Archiving

Archiving will be authorised by the ECAL trial office at BCTU on behalf of the Sponsor following submission of the end of trial report.

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g., signed ICFs, Investigator Site Files, Laboratory Files, participants' hospital notes, copies of CRFs) at their site are securely retained for the contractual period. Archiving will be authorised by BCTU on behalf of UoB following submission of the end of trial report. No documents should be destroyed without prior approval from the Sponsor or their delegate.

The TMF will be stored at BCTU for at least 3 years after the end of the trial. Long-term offsite data archiving facilities will be considered for storage after this time; data will be stored securely and confidentially for at least 25 years. BCTU has standard processes for both hard copy and computer database legacy archiving.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Site set-up and initiation

All PIs will be asked to sign the necessary agreements including Protocol PI signature page and a trial Site Signature and Delegation log between the PI and the Trial Office and supply a current CV and GCP certificate. All members of the site research team are required to sign the Site Signature and Delegation Log, which details which tasks have been delegated to them by the PI. The Site Signature and Delegation Log should be kept up to date by the PI. It is the PI's responsibility to inform the Trial Office of any changes in the site research team.

Prior to commencing recruitment, each recruiting site will undergo a process of site initiation, either a face-to-face meeting or via teleconference, at which key members of the site research team are required to attend covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF and a Laboratory File containing essential documentation, instructions, and other documentation required for the conduct of the trial.

13.2 Monitoring

The central and on-site monitoring requirements for this trial have been developed in conjunction with the trial specific risk assessment and are documented in the trial specific monitoring plan.

13.2.1 On-site monitoring

For this trial, all sites will be monitored in accordance with the trial risk assessment and monitoring plan. Any monitoring activities will be reported to the Trial Office and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered. PIs and site research teams will allow the ECAL trial staff access to source documents as requested. The monitoring will be conducted by BCTU/UoB or Sponsor staff.

13.2.2 Central monitoring

The Trial Office will check received ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing at a frequency and intensity determined by the Data

Management Plan. Sites will be sent queries through the REDCap trial database requesting missing data or clarification of inconsistencies or discrepancies.

13.2.3 Sample monitoring

Remote monitoring of sites regarding collection and management of blood samples will be conducted by BCTU via reviewing relevant CRFs. On-site monitoring will be triggered should there be a high amount of missing data for full blood count, and if there is a high rate of haemolysis in samples returned.

Long term sample storage at the primary site (University of Birmingham Research Laboratories, QEHB) will be monitored for temperature variance which may impact sample integrity 24 hours a day by electronic monitoring system, with established notification hierarchy should freezer temperature move beyond pre-set limits. Samples collected and electronic monitoring records will be maintained for 5 years after collection. Sample storage will be recorded in ECAL lab file, maintained by the EME safety sub-study technician.

13.2.4 Central stop smoking service/ pharmacy monitoring

The Trial Office will check products dispense log for compliance with what has been requested at a frequency and intensity determined by the Data Management Plan. Further monitoring will be triggered should there be a high amount of inconsistent or missing data on products allocated.

13.3 Audit and inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site and provide direct access to source data/documents. The Principal Investigator will comply with these visits and any required follow-up. Sites are also requested to notify the Trial Office of any relevant inspections or local audits.

13.4 Notification of Serious Breaches

In accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial or of the protocol relating to that trial, within 7 days of becoming aware of that breach. For the purposes of this regulation, a “serious breach” is a breach which is likely to affect:

- the safety or physical or mental integrity of the participants of the trial;
- the scientific value of the trial.

Sites are therefore requested to notify the Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol as soon as they become aware of them. Where the Trial Office is investigating whether or not a serious breach has occurred, sites are also requested to co-operate with the Trial Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

14. END OF TRIAL DEFINITION

The end of trial will be the date of the last data capture including resolution of data queries. This will allow sufficient time for the completion of protocol procedures, data collection and input and data cleaning. The Trial Office will notify the REC, MHRA and the Sponsor within 90 days of the end of trial. Where the trial has terminated early, the Trial Office will notify the MHRA and REC within 15 days of the end of trial. The Trial Office will provide the REC, MHRA and the Sponsor with a summary of the clinical trial report within 12 months of the end of trial.

15. STATISTICAL CONSIDERATIONS

15.1 Sample size

The justification for the sample size is based on a control group event rate of 8%. This is the expected proportion of participants who will have quit smoking at 52 weeks using combination NRT and behavioural support. The most recent data from specialist stop smoking services report a 10% quit rate with varenicline and behavioural support at 52 weeks, and combination NRT has been shown in a network meta-analysis to have similar effectiveness to varenicline.[56] However, quit rates are generally lower in COPD patients than in the general population[8] and so a value of 8% was deemed clinically appropriate.

To detect a difference of 6% (i.e. a quit rate of 14%) between the combination NRT and EC arms using the standard method of difference between proportions and assuming 90% power and a type I error rate of 5%, a total of 603 participants per group will need to be randomised, 1206 in total. Assuming and adjusting for a 3% loss to follow-up/ drop-out rate (based on local cohort data for mortality) and rounding up, 1250 participants will need to be recruited.

15.2 Analysis of outcomes

A Statistical Analysis Plan (SAP) for the trial will be produced and will provide a more comprehensive description of the planned statistical analyses for the trial. A brief outline of these analyses is given below.

The primary comparison groups will be composed of those randomised to the control treatment (combination NRT and behavioural support) versus those randomised to the intervention (Electronic cigarette and behavioural support). In the first instance, all analyses will be based on the intention to treat principle, i.e. all participants will be analysed in the treatment group to which they were randomised irrespective of adherence or other protocol deviation. For all outcomes, appropriate summary statistics and differences between groups, e.g. mean differences, relative risks will be presented, with 95% confidence intervals and p-values from two-sided tests also given. Outcomes will be adjusted for the minimisation variables listed in section 7.1.1 where possible. No adjustment for multiple comparisons will be made.

15.2.1 Primary outcome(s)

The primary outcome for the ECAL trial is smoking abstinence since the TQD biologically validated (exhaled CO<8ppm) at 52 weeks post quit date. This will be measured in accordance with the Russell Standard[1] which is the accepted standard for smoking abstinence in trials of smoking cessation interventions.

The data for this outcome are binary, and therefore will be summarised using the number and percentage of participants in each category by intervention arm. An adjusted relative risk and 95% confidence interval will be estimated from a log-binomial regression model and the p-value from the associated model will be produced and used to determine statistical significance. We will also present the adjusted risk difference and the corresponding 95% confidence interval.

15.2.2 Secondary outcomes

The secondary outcomes consist of continuous, binary, and count data types.

Secondary outcomes that are binary in nature will be analysed using the same statistical methods described above for the primary outcome.

Secondary outcomes that are continuous will be summarised using the mean and standard deviation for each intervention arm. Minimum and maximum values will also be presented. The

difference between the group means and associated 95% confidence intervals at each time-point will be estimated through the use of a repeated measures mixed-effects linear regression model. All post-randomisation assessment times will be included. Parameters allowing for participant, treatment group, time variable, the randomisation minimisation variables and the baseline score will be included (all as fixed effects). Time will be assumed to be a categorical (fixed) variable. To allow for a varying treatment effect over time, a time by treatment interaction parameter will be included in the model. Estimates of differences between groups at each post-randomisation time-point will be taken from the model including this interaction parameter. Results will be presented as an adjusted mean difference and the associated 95% confidence interval. Longitudinal plots of the data over time will be constructed for visual presentation of the data.

Secondary outcomes that involve count data will be analysed using a Poisson regression model (or negative binomial regression if there is evidence of overdispersion) with an offset for the length of time the participant was in the trial included in the model, to obtain an adjusted incidence rate ratio and 95% confidence interval. The p-value from the associated model will be produced and used to determine statistical significance.

Validated questionnaires will be scored using the methods recommended by the authors.

15.3 Planned subgroup analyses

Subgroup analyses will be limited to the same variables used in the minimisation algorithm (see Section7 – RANDOMISATION and BLINDING) and performed on the primary outcome only. The effects of these subgroups will be examined by including an intervention group by subgroup interaction parameter in the regression model, which will be presented alongside the effect estimate and 95% confidence interval within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

15.4 Missing data and sensitivity analyses

Every attempt will be made to collect full follow-up data on all trial participants; it is thus anticipated that missing data will be minimal. It is standard practice in smoking cessation trials to treat missing cessation data as a treatment failure (unless the participant has died or is untraceable),[1] and so trial participants with missing primary outcome data will be deemed to have not quit smoking at 52 weeks.[1]

For the primary outcome, we will conduct three pre-specified sensitivity analyses: (1) a per-protocol analysis that excludes participants who did not start product use and did not set a quit date, or never established contact with the trial team (2) an analysis in which we exclude abstinent participants who use non-allocated products (that is, e-cigarettes in the NRT arm and NRT in the e-cigarette arm) for at least 5 consecutive days during the 4 weeks after the TQD or who reported current use at the 52 week follow up or regular use for at least 1 week or occasional use for at least 3 weeks during the 52 week follow up from TQD, and (3) an analysis in which participants who abstain from smoking using a non-allocated product will be coded as non-abstainers.

Full details will be included in the Statistical Analysis Plan.

15.5 Planned final analyses

The primary analysis for the trial will occur once all participants have completed the 52-week assessment and corresponding outcome data has been entered onto the trial database and validated as being ready for analysis. This analysis will include data items up to and including the 52-week assessment and no further.

16. HEALTH ECONOMICS

A separate Health Economics Analysis Plan will be produced and will provide a more comprehensive description of the planned analyses, and reporting of methods and results will conform to the CHEERS guidelines.

A brief outline of these analyses is given below.

16.1 Economic evaluation

The economic evaluation will comprise of a within-trial evaluation using data over 52 weeks follow up, and a model-based evaluation, extrapolating beyond the trial time frame. For both analyses, the base-case evaluation will be conducted from a UK NHS perspective, including only those costs incurred by the health service. A secondary analysis will take a broader perspective and include patient out of pocket costs.

16.2 Trial based economic evaluation

Information on COPD-related resource use will be collected via patient questionnaires at 26 and 52 weeks and study case report forms. Questions will request information regarding primary care visits (e.g. GP, nurse), visits to other health care professionals (e.g. for pulmonary rehabilitation), medications (including antibiotics for exacerbations), secondary care consultations, hospital admissions including emergency visits and inpatient stays. The recall period in each patient questionnaire will be the previous 6 months. Data will be collected within the trial on all resources related to EC and NRT provided by the trial, initial consultations for advice and ongoing standard smoking cessation support by telephone. Patient will also be asked to recall out of pocket costs for items purchased for the continued use of EC, and any other smoking cessation products purchased. Unit costs from standard UK sources will be sought for all health care resource use items. In order to calculate QALYs, the EQ-5D-5L questionnaire will be administered to patients at baseline and at 4, 26 and 52 weeks. The crosswalk value set will be applied to patient responses to obtain utility scores, in line with current NICE recommendations. The more recent English value set will be used in a sensitivity analysis.

QALYs will be calculated using responses to the EQ-5D-5L, using the “area under the curve” approach. Unit costs will be applied to all health care resource use items, and mean resource use (for each category of health care usage) and mean total costs will be calculated for all trial participants. Multiple imputation will be used to impute all missing values for the EQ-5D and total cost estimates for non-responders. Incremental cost-effectiveness and cost-utility analyses will be undertaken to estimate the incremental cost per quitter and cost per QALY gained respectively, with adjustment for baseline covariates. The robustness of the results will be explored using sensitivity analysis. Cost-effectiveness acceptability curves will also be produced to reflect the probability the intervention will be cost effective at different cost per QALY willingness to pay thresholds.

16.3 Model-based economic evaluation

Decision modelling will also be undertaken to extend the within-trial results beyond 12 months follow up, to assess longer-term impact of interventions on exacerbations and disease progression. The purpose of the model is to extrapolate costs and QALYs over a lifetime time horizon to calculate the long-term cost-effectiveness (cost per QALY) of the intervention, from an NHS perspective and a broader perspective (including out of pocket costs), with discounting of costs and outcomes at 3.5%. This will be a Markov model which allows the representation of health states related to the condition (using GOLD stages of disease), disease progression and exacerbations. The model will be subject to deterministic and probabilistic sensitivity analysis.

Cost-effectiveness planes and cost-effectiveness acceptability curves will be presented to show the probability the intervention is cost-effective at different cost/QALY thresholds.

17. SUB-STUDIES

We will use data collected during the trial to conduct pre-specified cohort analyses. COPD patients from the RCT that fulfil the criteria for vaper, quitter and smokers will be included in the lung health and wellbeing sub study cohort analyses. We will model mean change or change in proportion in the outcomes listed for these sub studies (see section 9.4 and 9.5). Adjustments will be made for confounders and the baseline value of the outcome variable in the case of linear regression. Full details of the analysis will be included in a separate cohort sub-study SAP.

18. TRIAL ORGANISATIONAL STRUCTURE

18.1 Sponsor

The Sponsor for this trial is University of Birmingham (UoB).

18.2 Coordinating centre

The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit (BCTU), based at UoB.

18.3 Trial Management Group

The Trial Management Group comprises individuals responsible for the day-to-day management of the trial, including the CI, statistician(s), trial team leader, trial manager, data manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet sufficiently frequently to fulfil its function.

18.4 Co-investigator group

The Co-investigator group, an extended TMG, will comprise all members of the co-applicant group and the members of the TMG to review progress, troubleshoot and plan strategically.

18.5 Trial Steering Committee

A Trial Steering Committee (TSC), comprising independent and non-independent members, will be established for the ECAL trial and will meet as required depending on the needs of the trial. Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the role of the TSC is to provide oversight of the trial. The TSC will monitor trial progress and conduct and provide advice on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC). The TSC will operate in accordance with a trial specific TSC Charter.

18.6 Data Monitoring Committee

The role of the independent DMC is to monitor the trial data and make recommendations to the TSC on whether there are any ethical or safety reasons as to why the trial should not continue or whether it needs to be modified. To this end, data on safety outcomes and (where appropriate) primary and major secondary outcomes will be supplied to the DMC during the trial. Reports will be supplied in confidence.

The DMC will operate in accordance with a trial specific DMC Charter which will define the membership, roles and responsibilities of the DMC. The DMC will meet at least annually as a minimum. Additional meetings may be called if needed e.g., recruitment is faster than anticipated or a safety issue is identified.

18.7 Finance

The research costs of the ECAL trial are funded by National Institute of Health and Care Research (NIHR), Health Technology Assessment Programme (HTA) Ref: 129593, awarded to Dr Amanda Farley and Prof. David Thickett. The blood measures for the Lung health sub-study is funded by the NIHR Efficacy and Mechanisms Evaluation (EME) programme Ref 131600, awarded to Dr Aaron Scott.

The trial has been designed to minimise extra 'service support' costs for participating sites as far as possible. Additional costs, service support costs and excess intervention costs associated with the trial, e.g., gaining consent, are estimated in the Schedule of Events. These costs should be met by accessing the Trust's Support for Science budget via the Local Comprehensive Research Network.

The ECAL Trial is an eligible NIHR portfolio study.

19. ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant subsequent amendments), which include, but are not limited to, the Medicines for Human Use Clinical Trials 2004, Data Protection Act 2018.

This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations and according to the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments).

The protocol will be submitted to and approved by the REC prior to the start of the trial. All correspondence with the MHRA and/or REC will be retained in the TMF/ISF, and an annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given by the REC, and annually until the trial is declared ended. A trial-specific risk assessment and monitoring plan will be developed before submission to the REC and will be reviewed regularly during the trial.

Before any participants are enrolled into the trial, the PI at each site is required to obtain the necessary local approval.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

20. DATA PROTECTION AND CONFIDENTIALITY

Personal data and sensitive personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 (and subsequent amendments). Personal data categories that will be collected and analysed include name, date of birth, NHS number, email or postal address, health information, medical history.

Participants will be identified by their unique trial identification number and initials on CRFs and on any correspondence with the Trial Office. Participants will acknowledge the transfer and storage of their informed consent form to the Trial Office. This will be used to perform central monitoring of the consent process. Participants will be asked to consent to Queen Mary University of London having access to their personal data for the purpose of delivering the behavioural support calls and conducting the 4 week and 26 week follow ups.

In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records. Representatives of the ECAL trial team and sponsor may be required to have access to participants' notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times. The Trial Office will maintain the confidentiality of all participant data and will not disclose information by which participants may be identified to any third party.

21. FINANCIAL AND OTHER COMPETING INTERESTS

There are no financial or other competing interests related to the results of this trial. Members of the TSC and DMC are required to provide declarations on potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

22. INSURANCE AND INDEMNITY

UoB has in place Clinical Trials indemnity coverage for this trial which provides cover to UoB for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at UoB's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

UoB is independent of any pharmaceutical company and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

23. POST-TRIAL CARE

All patients will continue to receive standard medical care during and following participation in the clinical trial. There are no interventions that participants will be prevented from accessing after their participation in the trial has been completed. The participants continued treatment will be decided by the clinical care team with reference to current NICE guidelines.

24. ACCESS TO FINAL DATASET

The final dataset will be available to members of the Trial Management and co-applicant group who need access to the data to undertake the final analyses.

Requests for data generated during this trial will be considered by BCTU. Data will typically be available six months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data).

Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI and, where appropriate (or in absence of the CI) any of the following: the Trial Sponsor, the relevant Trial Management Group (TMG), and independent TSC.

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers transfer of participant identifiable information. Any data transfer will use a secure and encrypted method.

25. PUBLICATION PLAN

Outputs from this trial will be submitted for publication in peer reviewed journals and the findings of the trial will be made public. Manuscripts will be prepared by the writing group as defined in the trial publication plan. Manuscripts should be submitted to the TMG/co-applicant group in a timely fashion and in advance of being submitted for publication to allow time for review.

In all publications, authors should acknowledge that the trial was performed with the support of National Institute for Health and Care Research (NIHR), University of Birmingham, Queen Mary University of London and BCTU. Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site.

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APPENDIX 1

Outcomes by study objectives

	Main trial*	Health economic analysis*	Lung health sub-study**	Wellbeing sub-study**
Abstinence from smoking since target quit date (TQD) biochemically validated (exhaled CO<8ppm) at 52 weeks post TQD, defined in accordance with the Russell Standard[1]	√ (Primary)			
Abstinence from smoking for at least 26 weeks biochemically validated (exhaled CO<8ppm) at 52 weeks	√			
7-day point prevalence abstinence from smoking biochemically validated (exhaled CO<8ppm) at 52 weeks	√			
Self-reported abstinence from smoking for at least 26 weeks at 52 weeks	√			
Self-reported 7-day point prevalence abstinence from smoking at 4, 26 and 52 weeks	√			
Reduction in cigarettes smoked (self-report of any and > 50% reduction from baseline to 52 weeks, confirmed by reductions in expired CO readings at 52 weeks)	√			
Reduction in cigarettes smoked (self-report of any and > 50% reduction from baseline to 26/52 weeks)	√			
Continued use of allocated product at 4, 26 and 52 weeks	√			
Withdrawal symptoms and urges to smoke (change from baseline to 1/2/3/4 weeks) measured using the mood and physical symptom scale (MPSS)	√			
COPD Symptoms (change from baseline to 4/26/52 weeks) measured using COPD Assessment Test (CAT) and the Clinical COPD Questionnaire (CCQ)	√		√	
Number of COPD exacerbations over the past 52 weeks (from baseline to 52 weeks)	√		√	
Number of self-reported upper respiratory tract infections over the past 52 weeks (from baseline to 52 weeks)	√		√	
Post bronchodilator spirometry (FEV_1, FVC and MMEF change from baseline to 52 weeks). · Forced Expiratory Volume in 1 Second (FEV_1) · Forced Vital Capacity (FVC) · Mean Mid-Expiratory Flow (MMEF)	√		√	

Health-related quality of life (EQ-5D-5L) (change from baseline to 4/26/52 weeks)		√		
Use of healthcare resources and costs (measured at 26 and 52 weeks)		√		
Cost-effectiveness based on cost per quitter and cost per Quality-Adjusted Life-Year (QALY) at 52 weeks, and modelled cost per QALY over patient lifetime		√		
Full blood count (total and differential WBC $x10^9$/L)			√	
Serum/plasma biomarkers such as but not restricted to cytokines IL-6, IL-8, TNF-α; antimicrobial peptides; and markers of proteinase activity (change from baseline to 52 weeks)			√	
Toxicant analysis; to include toxicants such as formaldehyde, acetaldehyde, acrolein (change from baseline to 52 weeks)			√	
Anxiety - HADS (change from baseline to 52 weeks)				√
Depression - HADS (change from baseline to 52 weeks)				√
Mixed anxiety and depression - EQ-5D-5L (change from baseline to 52 weeks)				√
Breathing related depression and social quality of life - CCQ (change from baseline to 52 weeks)				√

*In all trial participants, comparing outcomes by trial arm

**In participants in the sub-studies only, comparing outcomes by exposure group (Exclusive EC user, quitter, smoker)