

Study Protocol

Vascular **E**ffect**S** of reg**U**lar cigarettes **V**ersus electron**I**c cigarette **U**Se

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VESUVIUS Study

Protocol Version 5.0 08-05-2018

PROTOCOL APPROVAL

VESUVIUS: Vascular EffectS of regUlar cigarettes Versus electronIc cigarette Use

Signatures

By signing this document I am confirming that I have read, understood and approve the protocol for the above study.

Dr Jacob George

Signature

Date

Chief Investigator

Dr Daniel Levin

Signature

Date

Individual Responsible for
Statistical Review

LIST OF ABBREVIATIONS

GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
ISF	Investigator Site File
TMF	Trial Master File
SOP	Standard Operating Procedure
CRF	Case Report Form
AE	Adverse Event
SAE	Serious Adverse Event
AR	Adverse Reaction
UAR	Unexpected Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
CNORIS	Clinical Negligence and Other Risks Scheme
SmPC	Summary of Product Characteristics
NRES	National Research Ethics Service
REC	Research Ethics Committee
MHRA	Medicines and Healthcare Products Regulatory Agency

SUMMARY

Electronic cigarettes (EC) are gaining popularity as an alternative to Traditional Cigarettes (TC). Despite not containing all the harmful substances seen in TC, EC are known to contain impurities that may have a detrimental impact on human health. The effects of ECs compared with TC on vascular function, inflammation and oxidative stress are unknown. It is increasingly recognised that nicotine itself has significant atherothrombotic effects. Therefore, clinicians are unable to confidently recommend ECs as a less risky alternative to TC.

Hypothesis: Endothelial function will be improved on EC compared to TC when measured by flow mediated dilatation (FMD).

Aims: To assess the effects of EC-nicotine and EC-nicotine free on endothelial function as compared to TC.

Design: Single centre, 2-cohort parallel group, randomised controlled trial. with a comparator TC arm

Population: ≥ 18 years old, current TC smokers. Excluding those with cardiovascular disease (hypertension allowed).

Interventions: 2 groups will be randomised to either EC-nicotine or EC-nicotine free for 4 weeks. 1 group of TC smokers will be recruited as a comparator arm

Outcomes: the primary outcome is the change in endothelial stiffness as measured by Flow Medicated Dilatation between the TC and EC-nicotine free groups. Secondary outcomes are change in endothelial stiffness between EC-nicotine free and EC-nicotine groups and change in oxidative stress between all 3 groups.

Assessments: performed at baseline and 4 weeks.

Samples size: 135 participants randomised to 2 groups EC-nicotine (n=45) and EC-nicotine free (n=45) plus a comparator arm of TC (n=45), will have a 80% power to detect an improvement in FMD of 2.0% and 1.0% in the EC-nicotine free and EC-nicotine groups respectively compared to the TC group at 5% significance. This allows for a 10%, 15%, and 20% drop-out rates in the TC, EC-nicotine & EC-nicotine-free groups respectively.

Statistical Analysis: Change in outcome measures between interventions will be assessed by a linear contrast test, and a linear regression including the baseline FMD level and experimental group as covariates.

Potential benefit: This study will provide further information on the potential use these devices and the risks and/or benefits associated with them, specifically in relation to vascular health.

1 INTRODUCTION

1.1 BACKGROUND & RATIONALE FOR STUDY

How safe are Electronic Cigarettes?

Electronic cigarettes, also known as e-cigarettes (EC), are increasingly widely used in an attempt to reduce rates of smoking traditional cigarettes (TC). There have been many controversial claims and counter-claims by various experts, social scientists and politicians in the media regarding its effectiveness and safety¹⁻³. The Medicines Health Regulatory Authority (MHRA) has stated that EC are to be licensed and regulated as part of European Union regulations which have imposed tougher restrictions on EC sales and marketing. The MHRA also state that although the amount of harmful carcinogens is only one thousandth of that contained in a TC, that the effects of these toxins, even at much smaller levels are unknown. They are known to be modestly effective in helping smokers to quit, with similar achievement of abstinence as with nicotine patches⁴. In one study, sustained 50% reduction in the number of cig/day at week-24 was shown in 32.5% of participants and sustained smoking abstinence at 24-weeks was observed in 22.5% participants⁵. A recent study looking at using ECs for smoking cessation, published in the Lancet, has concluded that “more research is urgently needed to clearly establish their overall benefits and harms at both individual and population levels⁶. EC are battery-powered devices that simulate tobacco smoking by using a heating element that vaporizes a liquid solution containing a mixture of nicotine and flavourings, while others release a flavoured vapour without nicotine. They are being marketed as a safer alternative to TC.

The benefits of EC on vascular function in terms of the reduction in tar and other contaminants that are present in TC are currently unknown. They are generally thought to deliver smaller quantities of nicotine compared with TC. Furthermore, TC contain >4,000 chemicals, including high levels of nicotine, carbon monoxide, acrolein, and pro-oxidant compounds⁷. However, recent evidence from the United States Food and Drug Administration (FDA) has shown that EC may not be completely harmless and in fact, may contain carcinogens such as nitrosamine and toxic chemicals such as diethylene glycol⁸ which are absent from TC. Subsequent analysis has also revealed the presence of tobacco-specific impurities suspected of being harmful to humans such as anabasine, myosmine, and β -nicotyrine in a majority of the samples tested⁹. Anabasine has been shown to experimentally affect adrenomedullary catecholamine excretion in rats¹⁰. Myosamine causes DNA damage through pyridyloxobutylation similar to the tobacco-specific nitrosamines (TSNA)¹¹. β -nicotyrine is an inactivator of CYP2A6, which is the Cytochrome P450 pathway for nicotine metabolism¹².

The impact of using EC on the cardiovascular system in particular is as yet unknown. The Medicines Health Regulatory Authority (MHRA) has stated that EC are to be licensed and regulated as part of the European Union regulations which have imposed tougher restrictions on EC sales and marketing¹³. The MHRA also state that the amount of harmful carcinogens mentioned in the paragraph above is only one thousandth of that contained in a TC but also concede that the effects of these

toxins, even at much smaller levels are unknown¹⁴. Following this, EC's are banned in health facilities in countries like the Republic of Ireland¹⁵ and parts of Wales¹⁶.

What are the known cardiovascular effects of nicotine?

While EC are sold on the premise that they are a much cleaner alternative to TC in that they do not contain harmful substances like tobacco and tar, they do nevertheless contain nicotine. What is increasingly clear is the detrimental effect of nicotine itself on vascular health. It is well established that nicotine increases the heart rate, blood pressure, platelet aggregation and pathological angiogenesis and down-regulation of nitric oxide^{17,18}. Recent studies have shown that nicotine (the addictive component of cigarettes) binds to high affinity nicotinic acetylcholine receptors (nAChRs) cell-surface receptors. This binding has been shown to accelerate the atherogenic process. Unlike free radicals, benzene and tar, nicotine is not thought to initiate plaque formation. However, it accelerates the growth of a pre-existing plaque. This is achieved by vascular smooth muscle cells (VSMC) proliferation, transforming growth factors (TGF) α and β , vascular endothelial growth factors (VEGF) and fibroblast growth factor (FGF) and concomitant suppression of apoptosis^{19,20}. Acute exposure to nicotine alone also worsens endothelial dysfunction in long term smokers²¹.

Further detrimental adverse vascular effects of TC

The complete adverse patho-biological effects of smoking TC are unknown. Aside from containing high amounts of nicotine and the attendant associated effects on plaque formation and atherosclerosis as described above, TC smoking is also known to impair endothelial function^{22,23} because it contains large amounts of harmful oxidants that cause oxidative stress damage to vascular endothelium²⁴, even in passive smokers²⁵ by nitric oxide (NO) uncoupling as well as arginase activation²⁶. Other effects include increasing production and release of endothelin, the up-regulation of matrix metalloproteinases²⁷. Finally, cigarette smoking is also thrombogenic in that it causes changes in platelet membrane fluidity and Na^+/K^+ ATPase activity²⁸ as well as increases platelet aggregation²⁹.

Amato et al³⁰ compared the effect of light versus heavy cigarettes on brachial artery FMD and found no difference in chronic smokers. This suggests that EC may not be the safe alternative that it is being promoted as but as of now, there is no data to suggest that this is true, hence this proposed study.

There are many ongoing debates on the role of EC and whether or not they are a legitimate replacement for TC. Therefore a clinical trial examining the cardiovascular effects of EC is needed to better inform regulatory authorities and governments regarding the possible cardiovascular risks or benefits of these devices. This proposed study will provide some preliminary useful information on which further definitive studies can later build on.

2 STUDY OBJECTIVES & OUTCOMES

Table 1: Primary Objectives and Outcome Measures

Primary Objective	Outcome Measure	Timepoints measured
To determine the effect of EC-nicotine free on vascular function as compare to TC.	Change in FMD between the TC group and the EC-nicotine free groups	0 and 4 weeks

Table 2: Secondary Objectives and Outcome Measures

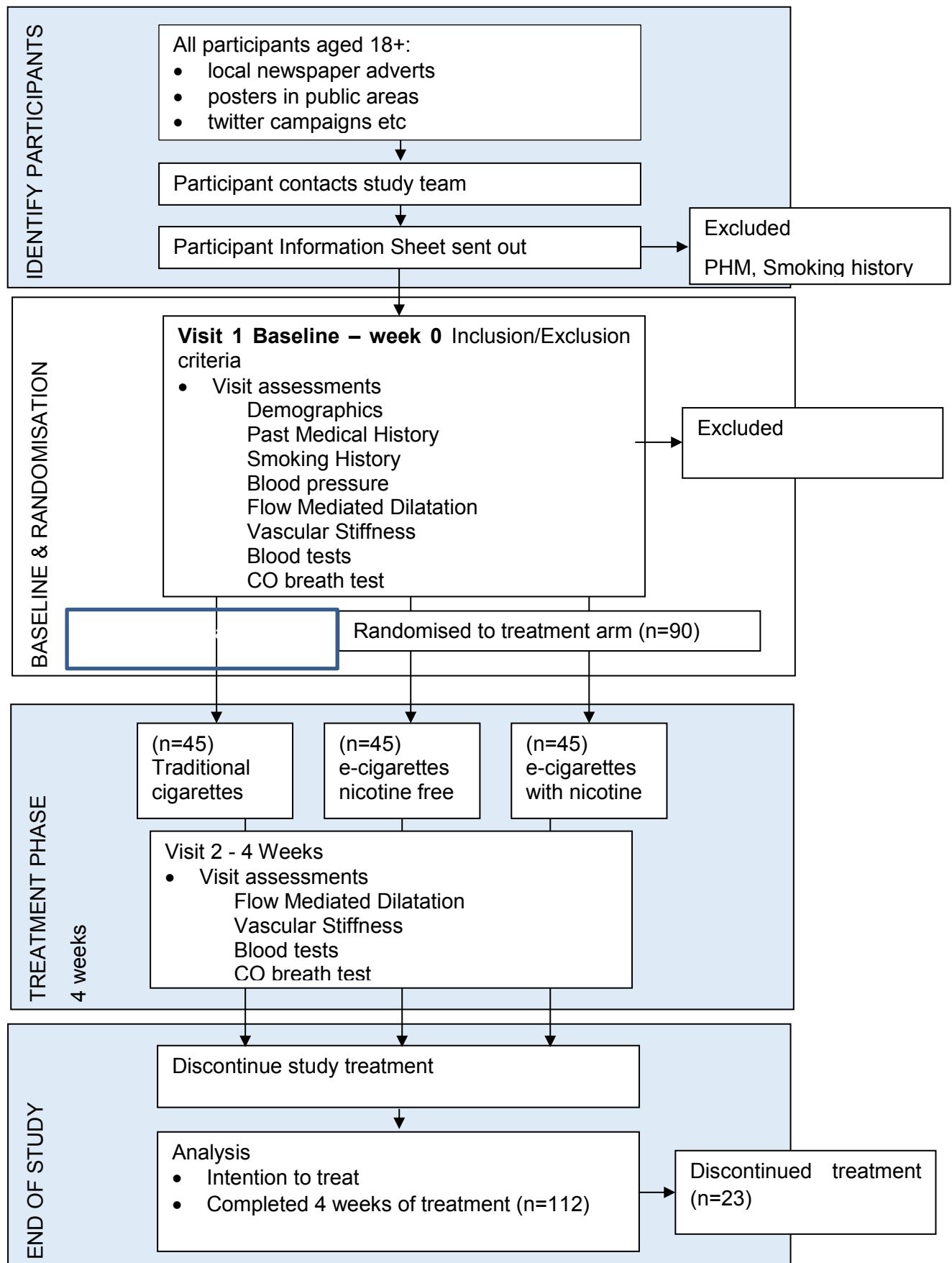
Secondary Objectives	Outcome Measures	Timepoints measured
To compare the effects of EC-nicotine vs EC-nicotine free on vascular function.	Change in FMD between EC-nicotine and EC-nicotine free groups	0 and 4 weeks
To compare the effects of EC-nicotine free vs TC on vascular function.	Change in Pulse Wave Velocity between the TC group and the EC-nicotine free groups. Change in Augmentation Index@75bpm between the TC group and the EC-nicotine free groups	0 and 4 weeks
To compare the effects of TC vs EC vs EC nicotine free on oxidative stress.	Change in total F2-Isoprostanes between the TC and EC groups	0 and 4 weeks

3 STUDY DESIGN

3.1 STUDY DESCRIPTION

VESUVIUS is a single-centre, (Tayside) randomized, 2-cohort parallel group of EC-nicotine and flavouring versus EC-nicotine free and flavouring versus comparator TC arm. These three arms will assess the differential benefits between (1) TC vs EC (2) the presence of nicotine in EC-nicotine versus EC-nicotine free.

3.2 STUDY FLOWCHART



3.3 STUDY MATRIX

Time	Baseline	Week 4[^]
Informed Consent	X	
Inclusion/exclusion criteria	X	
Demographics	X	
Past Medical History	X	
Smoking history	X	
Blood pressure	X	X
*Pregnancy test (if appropriate)	X	
Flow Mediated Dilatation	X	X
Vascular Stiffness	X	X
Blood test	X	X
CO Breath test	X	X
[∞] Smoking Diary	X	X
Randomisation	X	
Training on use of EC (if allocated)	X	
Supply EC (if allocated)	X	
Serious Adverse Events		X
Adherence		X
Provision of smoking cessation support details		X

[^] The week 4 visit will be carried out at 4 weeks \pm up to 10 days.

* Urine pregnancy testing on females of childbearing potential who do not abstain from sexiary will be given out at baseline and collected at the 4 week visit

Patients will also be supported as required by regular phone or text to encourage adherence.

Participants who complete the study will receive a monetary incentive in the form of shopping vouchers. vouchers will be payable at the end of the study to the maximum value of £40. this incentive is purely for those who complete both visits as a way to try and minimise dropouts. this will only work if payment is made on completion of study. however if the study team have to withdraw a participants a £20 of shopping voucher could be paid per visit attended

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

Number: 135 participants.

Recruitment period: 22 months

Dropout rate: it is anticipated that the dropout rates will vary depending on which group they have been randomised to. Assuming 10%, 15%, and 20% drop-out rates in the TC, EC-nicotine & EC-nicotine free groups respectively, we will require 135 participants to provide a final evaluable sample of 112 participants.

4.2 INCLUSION CRITERIA

- Aged 18 years and over
- Currently smoking ≥ 15 tobacco cigarettes per day for at least 2 years, or roll-up tobacco equivalent (cigar or pipe smokers will not be included).
- Willing to stop tobacco cigarettes for period of study if required
- Willing not to use electronic cigarettes if required
- Able to give informed consent

4.3 EXCLUSION CRITERIA

- Pregnant or lactating.
- Women of childbearing potential who do not abstain from sex or use effective contraception.
- On current prescribed medication for cardiovascular disease.
- History of cardiovascular disease (excluding hypertension), diabetes, active malignance or chronic renal disease.
- Nut allergy
- Participation in another clinical trial (other than observational trials and registries) with an investigational product and/or intervention within 30 days before visit 1.
- Use of electronic cigarettes within the last month.

Contraceptive advice to participants

Women of child-bearing potential, who do not abstain from sex, must be willing to have pregnancy testing prior to study entry. In addition, women of child bearing potential, who are sexually active, must be willing to use a form of a medically approved birth control method eg;

- Combined Oral Contraceptive Pill
- Placement of a intrauterine device - 'coil'
- Barrier methods of contraception: male condom only
- Established use of oral, injected, transdermal or implanted hormonal methods of contraception
- Male partner sterilisation (followed by the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Participants will be recruited via a publicity campaign using a range of methods:

- Posters/leaflets distributed in various places which may include:
 - Football/Bingo halls/ Bowling
 - Smoking shelters
 - Pubs
 - Hospital main entrances/ hospital clinics
 - Shopping Centres/Supermarkets/Pubs/etc.
 - Benefits offices/Post offices etc.
 - Sheltered Housing /Housing Associations
 - Community and charitable outreach programs
 - GP waiting rooms
 - Local company newsletters/payslips
- Advertisements in local newspapers and on local radio stations.
- Social media including twitter and Facebook.
- Invitation to those eligible on registered research volunteer databases held by the research team and the Scottish Health Research Register (SHARE).
- Potential participants will be identified via the Scottish Primary Care Research Network (SPCRN).
- Existing data-bases of smokers where permission has been granted to be approached for research purposes

5.2 CONSENTING PARTICIPANTS

Obtaining consent will be carried out by the PI, researcher or other local delegated individual in accordance with TASC SOP07: Obtaining Informed Consent from Potential Participants in Clinical Research

Potential participants who have seen the publicity campaign will be invited to contact the study team via phone or email. The researcher or other delegated individual will discuss the study via a phone call and assess for suitability. If the participant is thought to be suitable a participant information sheet (PIS) will be posted to the participant and a baseline visit arranged, all participants will be given at least 24 hours to consider their participation. If they decide to participate, informed consent will be taken by the researcher or other delegated individual and eligibility by all the criteria confirmed.

Where a participant requests to speak with a physician from the study team the consent process will not be completed until the participant had spoken to the physician and had all their questions answered to their satisfaction.

5.3 SCREENING FOR ELIGIBILITY

Participants who contact the research team expressing their interest in the study will be contacted and their suitability will be assessed as above prior to consent and booking a screening visit. Eligibility will be confirmed with the participant during the screening visit. The study visits will be performed within the Division of

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

The reason(s) for ineligibility will be explained to participants and any questions they have will be answered. They will be thanked for their participation and any relevant information from this will be added to their hospital notes and be communicated to their GP where the participant consents for this to happen.

5.5 RANDOMISATION

5.5.1 Randomisation

Randomisation will be carried out in a 1:1 fashion for the 2 randomised arms via a centrally controlled web-based GCP compliant randomisation system, TRUsT, run by Tayside Clinical Trials Unit (TCTU). To ensure balanced assignment across critical variables, a minimisation algorithm will be employed, using baseline age (≤ 40 years; > 40 years), sex (male; female) and smoking pack years (≤ 20 pack years; > 20 pack years). Randomisation will be performed by the PI, researcher or other local delegated individual.

Recruitment will stop when the required number is reached in each arm (maximum 45 per arm)

The TC arm will not be randomised.

To facilitate recruitment and minimise dropouts we propose to recruit the TC smoking arm as a separate non randomised group. Potential participants will be identified and approached in exactly the same ways as for the 2 EC arms. All participants will be asked if they wish to continue to smoke TC or to be randomised to one of the EC arms. This will enable us to recruit volunteers who would find it too difficult to stop their TC for 4 weeks. It will also avoid disappointment for those volunteers who are ready to stop smoking and do not wish to continue with their TC, which has the potential to lead to further dropouts. This is an unblinded study with the exception of the measurement of endothelial function and vascular stiffness which will be performed by a single blinded operator.

5.5.2 Intervention Allocation

Participants will initially be asked if they wish to continue smoking TC or if they would like to be randomised to one of the EC arms. Participants who wish to be randomised to one of the EC arms will be randomised to one of two groups in a 1:1 fashion. The groups will be:

- a) Switch to electronic cigarettes containing nicotine plus flavour
- b) Switch to electronic cigarettes containing flavour alone

Participants wishing to join the TC arm will be asked to continue their usual daily smoking habits, however, they will be asked not to smoke more than 30 cigarettes per day. Participants in this group will be asked not to use electronic cigarettes for the four week period of the trial.

For the groups receiving the electronic cigarettes, the Researcher or delegated individual will “dispense” the electronic cigarettes to participants. Instructions and explanation of how to use the electronic cigarettes will be given. Participants will be asked not to smoke tobacco cigarettes during the trial period.

5.5.3 Withdrawal procedures

When participants withdraw from active treatment the study team will ask them if they are willing to remain in the study and complete the study assessments.

If participants withdraw from the study and do not wish to return for study visits, contact with them will be maintained by the PI, trial manager, researcher or research assistant to ensure resolution of adverse event(s). If withdrawal is due to an AE it will be logged as such on the Adverse Event Log.

Participants are free to withdraw from the study at any time. The reasons, if known, will be recorded in the medical casenotes and CRF. Although a participant is not obliged to give reason(s) for withdrawing prematurely, if the participant appears lost to follow up, the CI will make a **reasonable** effort to ascertain the reason(s), while fully respecting the individual’s rights, and will demonstrate that everything possible was done in an attempt to find any participant lost to follow-up. Those lost to follow-up or withdrawn will be identified and a descriptive analysis of them provided, including the reasons for their loss and its relationship to treatment and outcome.

6 STUDY & SAFETY ASSESSMENTS

See Study Matrix, Section 3.3.

Flow Mediated Dilatation

Participants will be asked to fast from midnight the night before their visits, with the visit being performed in the morning. Participants who are electing to take part in one of the 2 randomized arms will also be asked not to smoke for 4 hours prior to their visits. Participants electing to take part in the tobacco cigarette arm do not have to withhold cigarettes for 4 hours but they will be asked to keep their smoking practises consisted before both visits. Endothelial function will be measured non-invasively at 0 and 1 month using the standard technique of flow mediated dilatation (FMD) of the brachial artery in response to hyperemia and to sublingual GTN. Brachial artery diameter and flow are determined by M mode and Doppler ultrasound as described by us previously³¹. FMD measurements are represented as change in arterial diameter from baseline. We will follow established protocols³². FMD is the technique we used recently to show a beneficial effect of allopurinol on endothelial function in subjects with chronic kidney disease³³ and in coronary artery disease³⁴. Our in house CV for FMD measurements is 3%. The FMD will be measured by a single experienced operator who will be blinded to treatment arms.

Vascular Stiffness

Pulse wave velocity (PWV) and pulse wave analysis (PWA) measurements including augmentation index corrected for heart rate (Aix@75) will be performed at baseline and 4 weeks using Sphygmocor™ as previously detailed³⁵. The FMD, PWV and PWA will be measured by a single experienced operator who will be blinded to treatment arms. These two measures have been validated as markers of cardiovascular risk³⁶.

Blood tests

The following blood tests will be carried out:

- 1) Oxidised LDL
- 2) High-sensitivity CRP
- 3) Platelet reactivity
- 4) Peripheral blood mononuclear cells for Oxidative stress NRf2 expression only (30 patients only, to be randomly selected).

Blood will also be stored, with patient consent, for future biomarker analysis.

7 DATA COLLECTION & MANAGEMENT

7.1 DATA COLLECTION

Data will be recorded at each visit (baseline and 4 weeks) on a paper CRF by the Researcher or delegated person and subsequently transcribed into the Data Management System database. The CRF will be used as source data but data relevant to a participant's general medical history will be recorded also in their medical casenotes. Data from the FMD and vascular stiffness will be entered into the Excel database as below.

7.2 DATA MANAGEMENT SYSTEM

Microsoft Excel will be used for data management and data management will be conducted as per TASC SOP48. The computer running EXCEL will be password protected and kept in a locked room. To prevent unauthorised access, computers will be accessible only to named individuals in the delegation log. Each individual will be given a password to log onto the computer. EXCEL will be used for the results, which are transcribed from paper CRFs. A spread sheet will be opened in EXCEL and will record only outcomes that are specified in the protocol. This spreadsheet will be saved on the University of Dundee secure server, backed up daily. A Disaster Recovery Plan is in place. No scripts or macros will be added to the EXCEL spreadsheet. The PI/Statistician responsible for data analysis will check the spreadsheet template for accuracy and format before any entry begins. Modification of the spreadsheet may occur until it is fit for purpose. The trial spreadsheet will be password protected and a copy of this password kept with the division secretary. Data entry will be a delegated responsibility. In order to be GCP compliant, data is entered the same day as visit or as soon as possible afterwards. The spreadsheet will be saved each time with date of entry thus an audit trail will be created on the EXCEL file. Subjects will be identified only by subject number(s) and age at consent. No participant identifiable information will be stored on the results spread sheet. Subjects will be cross checked with the Subject Log and/or Screening Log. As the paper CRF is completed, it will be checked for empty fields and fields outside of normal ranges. Data checking will include looking for fields outside of the subjects' normal ranges, which may lie within the normal expected general range. These will be highlighted by the Insert Comment facility available on EXCEL which also includes the name of the person highlighting the comment. All queries will be clarified with the PI or CI and any actions recorded. Any changes to the data in the CRF will be made a single line drawn through, initialled and dated. The original data will be clearly visible. The data on the EXCEL file will be always verifiable against the paper CRFs.

Verifying data

Data entry and checking will be undertaken by a single entry with a second look or a Single entry with a second individual reading aloud. The data entry and checking process will be decided according to risk. Data that is recorded in the CRF that is not source document in itself will be consistent with the source documents or the discrepancies explained. Checks will be made on all missing values and values out with normal or expected ranges and that values entered are of the correct type: i.e. numerical instead of text. Logical checks will be performed to ensure consistent reporting between relevant fields and that there are no differences between fields. Data checking will continue until all missing data and/or inconsistent values have been corrected or clarified. When data checking is complete, with no outstanding data queries, the database will be locked, using the Protect Worksheet function of EXCEL, as FINAL RESULTS. The EXCEL spreadsheet will remain archived on the Dundee University secure server for 10 years for the retention of essential documents, thereafter it will be deleted.

8 STATISTICS AND DATA ANALYSIS

8.1 SAMPLE SIZE CALCULATION

The primary endpoint measurement is change in brachial artery FMD, which is expressed as the maximum FMD percentage change from baseline. Based on our existing data for this measure (mean response 7.8%, SD=3.5%), and assuming mean FMD reductions of 2%, 1% and 0% in the EC-Nicotine-free, EC-Nicotine, and TC groups respectively with a SD of the change in FMD =3.0% (based on our previous study³¹), and a using a sample size calculation using Linear Contrast Tests³⁷ a sample size of 36 subjects in each group will have 80% power to detect an improvement in FMD of 2.0% and 1.0% in the EC-nicotine-free and EC-nicotine groups respectively compared to the TC group at 5% significance. Assuming 10%, 15%, and 20% drop-out rates in the TC, EC-nicotine & EC-nicotine-free groups respectively, we will require 135 completed subjects. **All drop-outs will be replaced to achieve 36 completed subjects in each group.**

8.2 PROPOSED ANALYSES

Descriptive statistics in the form of means and standard deviations for continuous variables and percentages and denominators will be tabulated for baseline and at each visit. The dependent variable will be assessed for approximation to a normal distribution and transformed if necessary. Pre-specified subgroup analyses will be completed by fitting the appropriate interaction term in the regression model and if significant outcomes will be presented separately by level of subgroup. The FMD response relationship will be assessed by a linear contrast test, and a linear regression including the baseline FMD level and experimental group as covariates.

The statistical analysis will be carried out in accordance to TASC SOP “Statistical Analysis Plans for Clinical Trials of Investigational Medicinal Products” by the study team statistician.

8.3 MISSING DATA

The primary analysis will be on a per protocol basis. **We will perform an intention to treat analysis as a secondary analysis.**..The extent of missing data will be examined

and the reason for drop-out ascertained. Multiple imputation will be used to impute missing values if the assumptions for missing at random (MAR) data are met.

8.4 TRANSFER OF DATA

Transfer of data out with the study site will not occur.

9 SERIOUS ADVERSE EVENTS

9.1 RECORDING AND REPORTING SAEs

Adverse events will not be recorded in this non-CTIMP study unless they are deemed as serious (SAE). All SAE will be recorded in a SAE Log.

A serious adverse event (SAE) is defined as an untoward occurrence that:

- results in death;
- is life-threatening;
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- or is otherwise considered medically significant by the investigator

Note: Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an SAE. However any serious adverse events occurring during such hospitalisation will be recorded.

An SAE occurring to a research participant will be reported to the main REC and Sponsor where in the opinion of the Chief Investigator (CI) the event was:

Related – that is, it resulted from administration of any of the research procedures, **and**

Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

Other SAE will not be reported.

SAEs will be reported as per HRA guidelines to the REC and Sponsor:

	Who	When	How	To whom
SAE	Chief Investigator (CI)	Within 15 days of the CI becoming aware of the event	SAE report form for non-CTIMPs	Main REC for the trial. Sponsor
Urgent safety measures	Chief Investigator (CI) or sponsor <i>Or exceptionally by local principal investigator (PI)</i>	(i) Immediately (ii) Within 3 days	(i) By telephone (ii) Notice in writing setting out the reasons for urgent safety measures and the plan for further action	Main REC, trial REC co-ordinator will acknowledge within 30 days Sponsor

10 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

10.1 TRIAL MANAGEMENT GROUP

The trial will be co-ordinated by a Trial Management Group, consisting of the grant holders, Trial Manager, Research Nurse and Senior Trial Manager (TCTU). The Trial Management Group will also act as the Trial Steering Committee (TSC). A Data Monitoring Committee is not considered necessary as this is a relatively small study involving a marketed intervention, this role will be undertaken by the TMG also.

10.2 TRIAL/STUDY MANAGEMENT

A Trial Coordinator will oversee the study and will be accountable to the CI. The Trial Coordinator or Research Nurse will be responsible for checking the CRFs for completeness, plausibility and consistency. However, this remains the overall responsibility of the CI. Any queries will be resolved by the CI or delegated member of the study team.

A study-specific Delegation Log will be prepared, detailing the responsibilities of each member of staff working on the study.

10.3 INSPECTION OF RECORDS

The CI, PIs and all institutions involved in the study will permit study related monitoring, audits, and REC review. The CI agrees to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation.

11 GOOD CLINICAL PRACTICE

11.1 ETHICAL CONDUCT OF THE STUDY

The study will be conducted in accordance with the principles of good clinical practice (GCP).

In addition to Sponsorship approval, a favourable ethical opinion will be obtained from an appropriate REC. Authorisation from an appropriate competent authority(s) and appropriate NHS R&D permissions(s) will be obtained prior to commencement of the study.

11.1.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access to study staff only. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee or Regulatory Authorities. The CI and study staff involved with this study will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

11.1.2 Data Protection

The CI and study staff involved with this study will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The CI and study staff will also adhere, if appropriate, to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality. Access to collated participant data will be restricted to the CI and appropriate study staff.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

11.1.3 Insurance and Indemnity

The University of Dundee and Tayside Health Board are Co-Sponsoring the study.

Insurance –The University of Dundee will obtain and hold a policy of Public Liability Insurance for legal liabilities arising from the study.

Tayside Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme (“CNORIS”) which covers the legal liability of Tayside in relation to the study.

Where the study involves University of Dundee staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

Indemnity The Co-Sponsors do not provide study participants with indemnity in relation to participation in the Study but have insurance for legal liability as described above.

12 STUDY CONDUCT RESPONSIBILITIES

12.1 PROTOCOL AMENDMENTS, DEVIATIONS AND BREACHES

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, REC and NHS R&D Office(s) as per TASC SOP 30 for: Amendments to Clinical Research Studies. Amendments to the protocol or other study docs will not be implemented without these approvals.

In the event that a CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

In the event that a serious breach of GCP is suspected, this will be reported to the Sponsor immediately using the form “Notification to Sponsor of Serious Breach or Serious Deviation”.

12.2 STUDY RECORD RETENTION

Archiving of study documents will be carried out as specified in TASC SOP 13: Archiving Clinical Research Documentation and Data. All study documentation will be kept for at least 10 years.

12.3 END OF STUDY

The end of study is defined as last patient last visit (LPLV). The Sponsor, CI and/or the TSC have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared.

13.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

13.3 PEER REVIEW

This study has been funded by the British Heart Foundation who have reviewed the grant application.

Additional peer review of the protocol occurs via the Sponsorship Committee. Resulting publications will be reviewed by the referees of the journal to which the paper (and its protocol) will be submitted.

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