Impact on Cardiovascular Function in Smokers Making a Quit Attempt Using E-cigarettes Compared with Smokers Making a Quit Attempt with Prescription Nicotine-Replacement Therapy (ISME-NRT)

You are being invited to take part in a research study as you are trying to give up smoking. Before you decide on participating, it is important for you to understand why the research is being done and what it will involve. Please take as much time as you need to read the following information carefully and discuss it with friends, relatives or your GP if you wish. It tells you about the study and will answer some questions that you may have.

PART 1 tells you the purpose of this study and what will happen to you if you take part.

PART 2 gives you more detailed information about how the study will be carried out.

Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part.

PART 1

What is the purpose of the study?

Smoking is the leading, preventable death-cause worldwide, being responsible for almost 100,000 deaths in the U.K., per year.

Cigarette smoke contains more than 9000 chemicals, the vast majority of which are released by tobacco combustion. Many people believe that it is the nicotine that causes the greatest harm. But in reality, it is other chemicals, heavy metals and small particles that have a major negative effect on health.

Therefore, it is important to encourage substitution of cigarettes with nicotine-based products with fewer chemicals as a means of quitting smoking. NHS has embraced this concept and has encouraged the use of pharmacological therapies, such as Nicotine Replacement Therapy. However, not many smokers trying to quit use these (only 23% in 2014). And many who manage to quit smoking initially go back to cigarettes within a short-period of time (75% within 6 months).

E-cigarettes or vaping devices use a battery to disperse a solution that usually contains propylene glycol or glycerine, water, flavouring and nicotine. They have been embraced by the British public (2.8 million users in 2016) and are the most frequently used means of "quitting smoking" aid amongst those who want to quit smoking (39.5%).

However, e-cigarettes are not without risks and research exploring the effects of e-cigarettes is limited, as little is known about their effects on the heart and veins or their medium- and longer-term cardiovascular disease risk.

Therefore, the purpose of this study is to explore the effects that e-cigarettes and Nicotine Replacement Therapy will have on the veins and the heart of smokers.

Why have I been invited to take part?

You have been invited because, according to our information, you are a current smoker and you are interested in stopping smoking.

Do I have to take part?

It is up to you to decide whether or not to take part. A decision not to take part will not count against you in any way. If you decide to take part, you can withdraw from the study at any point without giving any reason. If you withdraw, unless you object, we will still keep records relating to your participation, as this is valuable to the study.

What are the alternatives to taking part in this study?

Your doctor will advise on the best stop smoking options for you. If you choose not to take part in this study, then you can receive standard stop smoking support in the NHS system. These treatments include medication and behavioural change support.

What will happen if I take part?

We will only ask for your help for a maximum of 6 months. If you are eligible for the study and are happy to take part we will arrange for you to attend the Centre for Sport and Exercise Science at Sheffield Hallam University for a screening visit (Visit 1 - described below). You will be asked to sign a consent form agreeing to take part in the study. You will be given a copy of your signed consent form and this information sheet to keep. During the screening visit your eligibility for the study will be assessed in more detail. If you are eligible to take part then you will be asked to complete some tests to assess how your veins and arteries are functioning, your nicotine dependence, and general health. These tests are described in greater detail below. This appointment will take up to 90 minutes.

Participants will be then randomly assigned to one of three groups:

Group A will receive complimentary e-cigarettes (and refills for a 3-month period) with nicotine-rich liquid and support to stop smoking traditional cigarettes,

Group B will receive complimentary e-cigarettes (and refills for a 3-month period) with nicotine-free liquid and support to stop smoking traditional cigarettes,

Group C will be referred to the local NHS stop smoking clinics and will be able to receive Nicotine Replacement Therapy-based therapy and support to stop smoking traditional cigarettes.

Support to stop smoking will be the same format at all groups, with a minimum of 6 support sessions within the 3-month period, offering practical advice and support. These sessions will be delivered via Skype or over the phone, at a time and date convenient to you.

Which group you are put in depends on chance and is rather like tossing a coin. You will have an equal chance of being allocated to each of those groups. When the study is completed, the results are compared to see if there are any differences between the groups.

Taking part in the study would also mean coming to the research facility at Sheffield Hallam University for 4 visits over the next 6 months – one visit at the start of the study, the second visit 3 days after your nominated "stop smoking date", the third 3 months after your group allocation and the last visit 6 months after you are placed into a study group. These visits can be scheduled at a time and date to suit you.

A small group of participants will also be invited to speak to one of our researchers about their stop smoking experience. This short (30 minutes) discussion will take place either face-to-face or over the phone, at a time and date convenient for you. The discussion will be recorded and transcribed, with the record being deleted following transcription. Please note that we may use anonymized quotes from these conversations.

Visit 1 (week 1): Medical screening and baseline assessments (up to 90 minutes in total), Sheffield Hallam University.

During the first 15 minutes of this visit, we will discuss the study with you in detail. You will have the opportunity to ask questions and if you are happy to take part in the study we will request you to sign a consent form. During this visit we will ask a number of questions on your smoking history, current and previous medical history to confirm your suitability for the study. We will need to record your current medications, so please bring a list of all the medications that you are taking. We will also take your GPs contact details. As part of this visit, we will also measure your height, weight and your blood pressure. You are likely to experience a small degree of discomfort at the arm whilst the blood pressure cuffs are blown up.

If you are suitable for the study, the next 60-65 minutes will be for completing assessments of your health and fitness. Firstly, you will be asked to complete some questionnaires about your nicotine dependence, general health, physical activity and quality of life. This will enable us to assess your current cardiovascular disease risk. Secondly, we will assess how well the small blood vessels in your arm skin function using a test called laser Doppler flowmetry. Here, two small sticky patches will be applied to the skin of your forearm. Through these patches tiny quantities of two drugs (Acetylcholine Chloride and Sodium Nitroprusside) will be administered, which will cause local relaxation of the small blood vessels in your arm. Using probes connected to a computer, we will measure changes in skin blood flow. This procedure will be performed when you are lying down and relaxed. Thirdly, we will assess how your large arteries are functioning. A blood vessel in your upper arm will be imaged using ultrasound whilst a blood pressure cuff is inflated around your forearm for 5 minutes. Inflation of the cuff may result in a "pins and needles" sensation in the fingers, but this will go away when the cuff is released. Once the cuff is deflated arterial scanning will be maintained for a further 5 minutes.

Then we will take a drop of blood from your index finger, using a "finger prick test", which will help us calculate your total cholesterol/Low density lipoproteins ratio levels (as research shows that this is affected by smoking status). After that you will be asked to exhale in a tube, which will allow us to calculate the amount of carbon monoxide particles in your breath. This is a widely-used measurement to assess your smoking status.

In the final part of the session, you will receive instructions on how to complete a brief "smoking diary" (including your interactions with health services in relation to your stop smoking attempts and your continuous smoking/vaping habits) which we will give you. The information you provide in this diary will allow us to follow how your smoking habits change over time.

At this point you will be assigned to one of the three study groups.

Visit 2 (3 days after your "stop smoking date"): (60 minutes in total), Sheffield Hallam University.

During this visit, you will be asked to repeat the laser Doppler flowmetry and ultrasound assessments that were completed in the first visit. This will allow us to see if your randomly allocated therapy has offered any immediate physiological, effects.

Visit 3 (3 months after "quit date"): This is the end of the intervention assessment (75 minutes in total), Sheffield Hallam University

During this visit, you will be asked to repeat the assessments that were completed in the first study visit (all study questionnaires, vascular function tests, finger prick test, and carbon monoxide assessment). We will also take a copy of your "smoking diary".

Visit 4 (6 months after group allocation): Final follow-up assessment (75 minutes in total), Sheffield Hallam University

During this last study visit, you will be asked to repeat the assessments that were completed in the first study visit (all study questionnaires, vascular function tests, finger prick test, and carbon monoxide assessment). We will also take a copy of your "smoking diary".

PART 2

What are the possible advantages of taking part?

The aim of the study is to help you stop smoking. Statistics suggest that if you are successful in your stop smoking attempt, you will reduce your risk of developing a cardiovascular disease and die prematurely, while research also suggests that your quality of life will be improved. However, this is not guaranteed. The trial will also give us useful information which may be of benefit to others in the future and aid the way that stop smoking support is provided in the UK.

What are the possible disadvantages of taking part?

Participation in the study will require attending four study visits and taking part in assessments which will take some of your time. The procedures that we are using in this research are all well-established techniques which have been used in other patient groups in numerous research studies without any significant side effects being reported.

E-cigarettes have been considered as a stepping stone to stop smoking. However, there is some health risks associated with e-cigarettes including throat irritation and coughing, while the use of Nicotine Replacement Therapy has been associated with headaches, nausea and problems getting to sleep in the first few days. You are advised to think carefully - consulting your GP if necessary, whether participating in the study will be the right thing for you.

Are there any expenses or payments involved?

All participants in the e-cigarettes' groups will receive complimentary e-cigarettes' starter kits and refills for a 3-month period. We will also reimburse NHS prescription costs for the prescribed Nicotine Replacement Therapy supplies, for Group C participants. Additionally, we will arrange a free permit for on-site parking, for the assessment sessions, should you choose to drive.

If I decide to participate, will my GP be notified?

With your consent, we will inform your family doctor that you are taking part in this study, only in case our assessments reveal dangerously high blood pressure or cholesterol levels that require further medical assessment.

What if I change my mind during the study?

You are free to withdraw from the study at any time. If you decide to withdraw, we may ask you to consider attending one final assessment, but this is entirely optional. You can choose to leave the study at any time without having any further assessments. We would like to use all of your data up to the point of withdrawal as this will help with our analysis but you will be able to request that all records of your participation in the study to be removed from the study database. A decision not to carry on with the study will not affect how you will be treated.

Will my involvement in the study be kept confidential?

If you consent to take part in this study, the records obtained while you are in this study as well as related health records will remain strictly confidential at all times. The information will be held securely on paper and electronically at Sheffield Hallam University under the provisions of the 1998 Data Protection Act. Your name will not be passed to anyone else outside the research team or the sponsor. You will be allocated a trial number, which will be used as a code to identify you on all trial forms.

Your anonymized records will be available to people authorised to work on the trial but may also need to be made available to people authorised by the Research Sponsor (Sheffield Hallam University), which is the organisation responsible for ensuring that the study is carried out correctly. By signing the consent form you agree to this access for the current study and any further research that may be conducted in relation to it.

The information collected about you may also be shown anonymised to authorised people from the UK Regulatory Authority and Independent Ethics Committee; this is to ensure that the study is carried out to the highest possible scientific standards. All the study research team will have a duty of confidentiality to you as a research participant.

All material collected during interviews will be audio recorded and will be deleted following transcription. No identifiable information will be kept with the recording or transcript. Quotes from the interview may be taken word for word for reports, but you will be referred to as a number, (for example, "Participant 3").

If you withdraw consent from further study involvement, unless you object, your data will remain on file and will be included in the final study analysis.

In line with Good Clinical Practice guidelines, at the end of the study, your data will be securely archived for a minimum of 7 years from the end of the study. Arrangements for confidential destruction will then be made after this time.

What will happen to the information from the study?

It is anticipated that the results of the study will be presented at scientific meetings and published in a scientific journal. The overall results will be available to you; however, it will not be possible to provide you with an individualised report of your performance.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might have suffered will be addressed. Detailed information on this will be given in Part 2.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

What if I have further questions or would like more information about the study?

If you would like more information about the study you are invited to contact:-

Dr Gareth Jones Sheffield Hallam University Tel 0114 225 4312

(HeartResearch@shu.ac.uk)

What happens if I have a complaint?

If you have any cause to complain about any aspect of the way in which you have been approached or treated during the course of this study, you can use the normal University

complaints procedure and contact the University Secretary and Registrar, Liz Winders, Tel 0114 225 2051. If you have complaints on concerns please contact the project co-ordinator Dr Markos Klonizakis (Tel: 0114 225 5697, e-mail: m.klonizakis@shu.ac.uk).

What if I am harmed?

In the event that something does go wrong and you are harmed during the research study, there are no special compensation arrangements. If you are harmed as a result of someone's negligence then you may have grounds for legal action for compensation, but you may have to pay your legal costs.

Who is organising and funding the research?

This study is being funded by Heart Research UK. Sheffield Hallam University is responsible for the conduct of the study. The investigators of this study will not receive any payment for conducting this research**.**

Who has reviewed the study?

All research undertaken in a university setting is looked at by an independent group of people called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed by the ethics committee of the Faculty of Health and Wellbeing of Sheffield Hallam University. For any further queries, you may contact Dr. Nicola Jordan-Mahy (Tel: 0114 225 3120, e-mail: n.jordan@shu.ac.uk).

Thank you for taking the time to read this information sheet and to consider this study.