Chief Investigator: Dr Ajay Gupta,
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Participant Information Sheet

SCRATCH – HTN

Sham **c**ontrolled **R**andomized Control Trial evaluating the Safety, Acceptability and Efficacy of **A**utonomic neuromodulation using **t**rans-**c**utaneous auricular sensory stimulation in uncontrolled **h**ypertensive patients: a pilot study evaluating a novel non-invasive device-based strategy (SCRATCH –HTN).

Participant Information Summary

We would like to invite you to take part in our clinical trial (clinical study) which aims to explore a new way of managing high blood pressure (BP), specifically in people who have raised blood pressures despite being on medication or who require an increase in drug treatment to control their blood pressure.

We're doing this study to see if the use of an external self-administered device (which stimulates the nerves controlling BP), is safe, easy to use and can improve control of high BP. If proven, the device may potentially provide an alternative option for BP treatment.

In this study, we would like to assess how effective the device is in the treatment of hypertension, whether it is comfortable to use, people feel safe whilst using the device and the treatment is acceptable.

Joining this study is entirely up to you. However, before you decide, we would like you to understand why the research is being done and what it would involve should you decide to take part. Please take your time to read the information below and do not hesitate to ask about anything that is not clear and/or if you would like to have more information.

Volunteer only if you have the time and are willing to complete the whole study. If you are interested in taking part, please speak to the nurse or clinician who will talk you through the information sheet at a more convenient time.

Introduction

What is this study about?

High blood pressure is the leading risk factor for death and illness from a cardiovascular event, and managing high BP is a key focus of treatment for cardiovascular diseases. Antihypertensive drugs (drugs that aim to lower BP) are widely available, however a high number of people with high BP fail to achieve a healthy BP value despite receiving 1 or more anti-hypertensive medications. In this study, a small battery operated medical device that stimulates the nerves that control BP will be self-administered by study participants with the aim to lower BP and treat people with drug-resistant high blood pressure.

There has been some good trial evidence- mainly using invasive methods such as renal denervation- that reducing output from nerves (sympathetic nervous system) that control flight-and fight response is successful in reducing blood pressure. In comparison, in this clinical study, participants themselves stimulate the nerves that naturally control the output from the sympathetic nervous system. We have previously done a proof-of-concept observational study on a handful of patients and have observed this method of non-invasively redressing the deranged balance of stimulatory and calming nerves may help reduce BP.

In this first clinical study, we hope to recruit about 63 participants. Participants will be randomly allocated to receive either an active or an inactive device, in a 2:1 ratio meaning that 2 out 3 participants will have an active device. This study is designed to be blinded which means that neither the clinical study team, nor the participants will know who will or have been allocated to which device (active or inactive).

If you decide to participate in the study, you will sign page 13 of this information sheet to demonstrate that you have an understanding of the study and that you are happy to participate in the main study.

In addition to the main study, we will invite 26 of the main study participants, into a sub-study. Participation in the sub-study is optional and does not affect the participation to the main study.

The sub-study is designed to do more in-depth tests to assess the lack of balance between your sympathetic (stimulatory) and parasympathetic (calming) nervous system that some of the hypertensive patients exhibit.

If you participate in the sub-study, we will do physiological tests and extra blood tests to study various biomarkers such as acetyl choline, in addition to the main study tests. These are mentioned in page 15. If you are happy to participate in the sub-study you will sign page 16 to provide us with your informed consent to participate.

CONTENTS

Why have you been invited to participate?

You have been selected because you have a raised (uncontrolled) BP, and you are on BP (anti-hypertensive) medications. You may also have any one of the following conditions such as diabetes, raised pulse rate, obesity, or another hormone related illness, which will qualify you to be eligible for this study.

Do you have to take part?

It is entirely up to you if you wish to participate this study. If once you join the study, you change your mind and wish to withdraw, you may do at any time without giving any reason for doing so.

The Study

What will the study involve?

If you decide to take part, we will first carry out a screening assessment to make sure you are suitable for the trial. If you are suitable, we will train you to use the study device. The study device is attached to a small area at the front of both of your ears (the tragus) and passes a very small electrical current to the nerves in your outer ear. This procedure is not painful, however you may or may not feel tingling/burning sensation, which you can control by lowering the voltage. If you participate in this study, you will be asked to use it daily for 30 minutes for 14 days. After the 14 days, you will use it once a week for 10 weeks. You will also be asked to keep a log book recording the use of the device and your health. You will be asked to use the device while resting/relaxing/ in sitting or lying position (for example while watching TV, listening to music *(but not whilst wearing a headphone or airpods or similar device)* or reading a book, or at the end of the day retiring to the bed. You should try to avoid any moderate or heavy physical activity (such as exercising, running, continuous walking or lifting weights etc.), while using the device. We will ask you to remain on your medication and not change it throughout the trial. You will need to make several visits to our outpatient clinic where we will be monitoring your health during the trial, carrying out health assessments and undertaking various tests. The study will consist of 5 outpatient visits; a screening visit, baseline/randomization visit, outpatient visit 3, outpatient visit 4 and end of study visit (Visit 5). You will also be contacted by the study team by phone, text or email to support you in undertaking the treatment and ensuring the equipment is working. You will receive these phone calls/emails/texts 3-4 times during the study and once 4 weeks after your end of study visit.

During your visits we will conduct a variety of assessments/tests as follows:

- Height, weight & waist measurements
- Vital signs – temperature, pulse, respiration rate, blood pressure
- 24 hour BP and heart monitoring
- Heart scans (Electrocardiogram, commonly known as ECG, and Echocardiogram (which is an ultrasound scan of the heart)
- Blood samples
- Urine sample
- Questionnaires:

Extent of adherence questionnaire (EoA) to confirm that you're taking your current medication and complying with your treatment regimen.
Insomnia Severity Index (ISI) to check your quality of sleep
Blinding questionnaire to ask you if you think you are receiving the active or the inactive treatment
Device Usability questionnaire to ask if it is easy and acceptable to use the device
Quality of Life Questionnaire (EQ-5D QoL) to check how well you are feeling after commencing this treatment

- Cognitive assessment: this assessment evaluates your mental abilities (such as memory and reaction time).

Please note that if you are a female of reproductive age, we will complete a urine and blood (serum) pregnancy test. This will be done at Screening and Baseline visits, and we will ask that you use accepted contraception methods until the end of your study participation (telephone phone call at Day 112). We ask this because SCRATCH is a research study testing the safety of the device and it is a regulatory requirement. If you are pregnant, nursing or planning to become pregnant within the next 6 months, you will not be able to take part in the study. If you become pregnant whilst on the study or within 4 months after your last study visit, we will need to to inform us so that we can report this to the safety authorities and ensure the safety and wellbeing of yourself and your foetus. We do not expect the device to have any serious side effects on the foetus, but to ensure this we will need to follow your pregnancy up until the birth, and again this is a regulatory requirement for the study.

Following is the detailed description of what will happen during the outpatient visits:

Visit 1 (Screening Visit)

During this visit, we'll explain this study to you, and you will be given the opportunity to ask any questions. If you decide to participate in the study, we will ask you to sign the informed consent form. We will then do different checks to assess whether you are suitable for this study. We'll ask you to provide us with information about your demographic, medical, social history and current medication. We will also do some clinical measurements, such as height, weight and waist circumference measurements, blood pressures, ECG, heart rate. We will also take blood and urine samples to check your health, and we will do a blood and urine pregnancy test, if you are female and of a reproductive age.
For this visit, we will ask you to come with your own medications and take those prior to the fitting of 24 hour blood pressure monitor.
During this visit, we'll also show you the device and show you how it works and we'll ask you to try a dummy run so you are comfortable with its usage.

Visit 2 (Day 0 of the study or baseline/randomization visit)

In this visit, we'll confirm if you're suitable to participate in the study. Aim of this visit is to collect all your 'baseline' health data before the commencement of this 'new' treatment, hence we sometimes call this also as baseline visit.

For this visit, we'll ask you to bring your own blood pressure medications. On that day, we will do the following assessments: BP measurement, weight, 24hr BP monitoring, 24-hour ECG monitoring ((with a Holter device, which you will wear and take home – you don't need to be in the clinic for 24 hours), echocardiogram (around this visit time), 6 minute walk test. We will also take a blood sample and a urine sample to check your health, and check hypertension parameters. If you are female and of a reproductive age, we will repeat the urine and blood (serum) pregnancy test.
We will also ask you if you're feeling well and if you have taken any other medications. We will also ask you to complete the questionnaires, such as EoA, ISI, EQ-5D questionnaires and do a cognitive assessment

During this visit we'll train you on how to use the device and tell you when to use it and how often. You will then be given a device allocated to you by the computer system. We will then ask you to use the device on yourself under-supervision. Once you are comfortable with the use of the device, you can take it home for subsequent administrations, as well as a device logbook, where you will be asked to write down when you used the device and for how long.

Visit 3 – Day 14

For this visit, we will again ask you to bring your medications and the device with you. We will ask you to not have taken your morning medication prior to the visit, and to take the medication after we've taken your BP measurements. We will take BP and heart rate measurements, ask you to do 6 minute walk test, and ask you questions about your health, and ask you to complete the ISI, Device usability, EoA questionnaires and you will complete cognitive assessment. You will also use the device and complete the device logbook. In this visit, we will review your medications, evaluate for any adverse effects, look at your log-book and technique of self-administration.

Visit 4 – Day 28

For this visit, we will again ask you to bring your medications and the device with you. We will ask you to not have taken your morning medication prior to the visit, and to take the medication after we've taken your BP measurements. In this visit, we'll take BP and heart rate measurements, including 24 hour monitoring (using the Holter device, just like in Visit 2), ask you to complete the 6 minute walk test, the cognitive assessment, and we will also take blood and urine samples for laboratory evaluations. You will also use the device and complete the device logbook, and complete the blinding questionnaire. In this visit, we will review your medications, evaluate for any adverse effects, look at your log-book and technique of self-administration.

Visit 5 (Day 84 – End of the Trial Visit)
For this visit, we will again ask you to bring your medications and the device with you. We will ask you to not have taken your morning medication prior to the visit, and to take the medication after we've taken your BP measurements. We will do the following assessments: blood pressures and heart rate measurements, 24-hour BP and ECG monitoring, heart scan (Echocardiogram), and will also do all the questionnaire-based assessments (EoA, ISI, EQ-5D QoL, and Blinding questionnaire), and you will complete the cognitive assessment. You will also use the device and complete the device logbook. In this visit, we will review your medications, evaluate for any adverse effects, look at your log-book and technique of self-administration. At the end of this visit you will be asked to return the study device.

Phone Call Follow-Up - Day112
Four weeks after the End of Study visit, you will receive a phone call, and will be asked to complete the ED-5D QoL Questionnaire over the phone. We will also assess for any adverse effects and take note of your medications.

What support can I expect?

Besides the clinic visits, we will also be contacting you on a regular basis by phone, text or email to support you in undertaking the treatment and ensuring the equipment is working. These include:

Phone Call 1 – Day 1-4
Following your visit 1, we'll call you after a week to enquire how are you doing with self-administered device treatment, and will assess for any adverse effects, take note of your medications, and remind you about the device administration procedure and use of log book.

Phone Call 2 – Day 7
On this day, we'll call you to enquire how are you doing with self-administered device treatment, and will assess for any adverse effects, take note of your medications, and remind you about the device administration procedure and use of log book.

Text/Email Reminder - **Day 42**
On this day you will receive a reminder to complete the device administration procedure and fill in the logbook.

Phone Call 3, Day 56
On this day, we'll call you to enquire how are you doing with self-administered device treatment, and will assess for any adverse effects, take note of your medications, and remind you about the device administration procedure and use of log book.

Text/Email Reminder – Day 70
You will receive a reminder to complete the device administration procedure and device logbook entry.

Further support we will offer:

- For any enquiries relating to your treatment or the study:
  - Study team telephone contact number available Monday – Friday, 8am-11pm.
  - Study team email contact.
- For any questions relating to the use of the device - Device team telephone contact number accessible 9am-11pm for the first five days of your trial.
- A video demonstrating how to use the device accessible through the study website.
- Access to frequently asked questions accessible through the study website.

Travel and/or subsidence costs?

If you participate in the trial you will receive up to £35 per visit for reasonable travel (to the outpatient clinic) and/or subsistence costs. You will need to provide us with receipts and/or evidence of expenses when you come to the outpatient clinic, so that we are able to process your payment.

What will I be expected to do?

- You will need to carry out this treatment for half an hour every day for two weeks, and then weekly for a further ten weeks.
- You will also need to fill in a logbook for 12 weeks that will record your times of using the device as well as any changes in your general health.
- We will ask you to attend clinic five times (screening visit, baseline visit, outpatient visit 3, outpatient visit 4 and end of study visit) where we will be monitoring your health and ask you to complete assessments as explained in the previous section.
  Participants randomised into the trial will be eligible to receive up to £35 per visit for reasonable travel and/or subsistence costs. Participants will receive payments even in the event of trial withdrawal, which will be pro-rated for the number of attended visits. Payment will be processed as per QMUL finance policy, provided that receipts and/or evidence of expense is given to Investigation site.
- During the study you will be asked to not change your current treatment regimen.
- On you outpatient visits days, you will be asked to not take your antihypertensive medication in the morning, but instead, bring it with you so you can take the medication in the clinic after we've taken your BP measurements.

What are the possible disadvantages or risks?

In this study, we are using a device which is available over the counter for other usage such as pain control. However, this is the first time we are using this device to stimulate nerves to control BP (hypertension). Specifically, we do not have any available data on side effects when using this device for BP control. Therefore, in this study we will be collecting data to help us assess how the use of the device affects BP.

We do have data on side effects when this device was used for pain control. In those studies, side effects were uncommon and included complaints such as local discomfort at the site, coughing, gastrointestinal discomfort, headaches, light-headedness, nausea, pain and/or local skin irritation. We do not know whether these reported complaints are directly related to the use of the device or whether occurrence of such side effects is coincidental.

If you are female and become pregnant whilst on the study or within 4 months after your last study visit, we will need to to inform us so that we can report this to the safety authorities and ensure the safety and wellbeing of yourself and your foetus. We do not expect the device to have any serious side effects on the foetus, but to ensure this we will need to follow your pregnancy up until the birth.

We do not think there are any major and/or significant disadvantages of taking part in this study. It is possible (but uncertain) whether participants will report any of the side effects (as above). Since 1 out of 3 participants will be on the inactive device, and in this study we do not change BP medication for 3 months (which is the entire study duration), some participants may continue to have high blood pressure. It is also possible (but uncertain) in certain cases there may be a significant fall in BP that may cause dizziness when suddenly standing up (postural hypotension). During the study, we want you to continue monitoring your blood pressures at home as you would normally do. However, we strongly suggest that when you do your BP monitoring, you should take three BP readings, one minute apart, while sitting, and record the lowest of the three readings. You can use your own schedule, but we do recommend that you do the BP monitoring two days per week, both in the morning and in the evening. If your lowest (of the 3 recordings) systolic blood pressure reading is higher than 170 mm Hg or the lowest diastolic blood pressure reading is higher than 115 mm Hg, you should inform the study team as soon as possible. If this happens the study team will monitor your BPs more closely. This is so that they can act promptly by escalating your blood pressure treatment if your systolic blood pressure becomes greater or equal to180 mm Hg or your diastolic blood pressure becomes higher than 120 mm Hg. The study team will also act if your systolic blood pressure is lower than 100 mm Hg, or you develop dizziness on standing up.

What are the benefits?

We anticipate all participants whether on an active or inactive device may benefit on blood pressure control, not only because of the device, but also the close monitoring by the study team (this commonly known as hawthorn effect – benefit for taking part in a clinical study). Furthermore, it is possible that the detailed assessments in the study, may flag some hidden (as yet undiscovered) health issues. If this happens, we will inform you and with your permission inform your health care provider. However, the foremost benefit of taking part in the study is to potentially discover a new mode of therapy to help people with hypertension which is used (externally) by themselves which, reduces the need for taking extra medications and ultimately will be benefit those who have side effects to oral BP medications.

What if something goes wrong?

At the first visit, we will give you your participant ID card which will have contact details for the study. You should always carry this card with you, whilst you are participating in the study.
If you have any health concerns regarding your treatment you should call the study team using the contact details given to you in the participant ID card or see your GP.

If you have any emergency you should seek assistance as appropriate via NHS helpline, visiting A&E or calling the emergency services.
If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action, but you may have to pay for it. Regardless of this if you wish to complain

about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

Data and Confidentiality

What does this mean?

The information we collect from you and about you such as your health records, test results, treatments etc. is called data. When this information is combined with personal information such as your name or NHS number it is known as identifiable data and there are special rules to keep this information safe and secure and only share it with people who need to know the relevant bits.

In this study your name will be removed from the research data and replaced with a code. This is called coded data, (pseudonymised data). For example, your blood test might be labelled with your code number instead of your name. It can be matched up with the rest of the data relating to you by the code. We will make sure any information that shows who you are is removed, when there is no information that could show who you are, this is called anonymous data

We follow the General Data Protection Regulation (GDPR) rules that allow researchers to use patient data to do research to make health and care better. According to these rules we have to let you know When companies do research to develop new treatments, they need to be able to prove that they need to use patient data for the research, and that they need to do the research to develop new treatments. In legal terms this means that they have a 'legitimate interest' in using patient data.

As a University and NHS body we are expected to do research as part of our job and may need to be able to prove that we need to use patient data for the research. In legal terms this means that we will use patient data as part of 'a task in the public interest'.

What information/data will be kept?

All information collected about you as a result of your participation in the study will be kept strictly confidential and will be used for the purposes of this research only. Your personal and medical information will be kept in a highly secure server within the study electronic data capture system (Castor EDC) and handled securely in accordance with the data protection law to ensure that all information about you is handled in the strictest confidence.

If you decide to take part in the study, you will be assigned a study ID at the baseline visit, so that no information that could identify you is entered in the study database. To randomise and enrol you in the study we will enter your initials and date of birth on the randomisation system (Sealed Envelope) and data capture system (CASTOR EDC). No personally identifying information about you will be shared with any third parties not directly involved with this research. If you agree to it, we will inform your GP of your participation in this study so that any medical decisions made by your GP account for any treatment you are receiving as part of this study.

Your blood and urine samples will be sent to the local NHS Trust laboratory, where they will be analysed, and destroyed according to the Trust protocols. We will also send some of the

samples to QMUL research laboratory, where they will assess them. We are also asking your permission to store your blood samples to evaluate them on basis of any new information, insight about any new biomarker of response, or for safety evaluation. These samples will be stored in the QMUL based laboratory freezer. After the full study completion (after taking into account any extensions) we will either transfer all stored blood samples to the Bart bioresource facility (more information about storage of samples in this facility can be found here http://www.bartsbioresource.org.uk/about/) or destroy them. Relevant health data may be transferred with the samples. No blood or body-fluid samples that contain any genetic material will be stored in local facility after the trial closure.

Who has access to your information?

If you consent to take part in the research your data and medical records may be inspected by the research team, the company sponsoring the research and any regulatory authority for the purpose of analysis and to check the study is carried out correctly.

If you agree to it, we will inform your GP of your participation in this study so that any medical decisions made by your GP account for any treatment you are receiving as part of this study.

Some of the pseudoanonymised data we collect about you may be sent to the device manufacturer, Afferent.

What happens at the end of the study?

What will happen to the data after the study is finished?

The data we collect from your assessments and tests will be recorded in your medical records and kept in accordance with NHS policy. The centre where you are taking part in the study will keep a copy of the research data along with your name, date of birth and/or NHS number. Queen Mary will only keep a coded copy of your research data for 25 years, without your name included. This is kept so the results can be checked.

Queen Mary or Barts NHS trust may use your study data (after removal of any personal identifiers such as your name and NHS number) in future research. Once your details like your name or NHS number have been removed, other researchers won't be able to contact you to ask you about future research. Your direct care provider and NHS staff will however continue to have access to your identifier data and some of the information collected for research purposes.

Any information that could show who you are will be held safely with strict limits on who can access it.

You may also have the choice for the hospital or researchers to keep your contact details and some of your health information, so they can invite you to take part in future clinical trials or other studies. It will not be given to other organisations or companies except for research.

What will happen to the results of the study?

We will make sure the reports about the study are written in a way that no-one can work out that you took part in the study. When the results of this study are available, they will be published in peer reviewed medical journals and used for medical presentations and conferences. They will also be published on the clinicalstrials.gov website.

What if new information becomes available?

Sometimes during a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your research doctor will make arrangements for your care to continue. If you decide to continue in the study, you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. If this is the case, he/she will explain the reasons and arrange for your care to continue.'

Who is funding the research?

This clinical trial is funded by the National Institute for Health Research (NIHR). The NIHR is funded by the Department of Health and Social Care and works in partnership with the NHS, universities, local government, other research funders, patients and the public, to enable world-class research that transforms people's lives, promotes economic growth and advances science.

Who has reviewed this study?

This research study has been independently reviewed and given favourable opinion by the West of Scotland REC 4 Research Ethics Committee Research and approved by the Medicines & Healthcare products Regulatory Agency (MHRA) to protect your safety, rights, wellbeing and dignity. Public and patient involvement (PPI) has also been involved in the review of the study and participated in the development of patient facing material.

Researchers must show that their research takes account of the views of patients and ordinary members of the public. They must also show how they protect the privacy of the people who take part. An NHS research ethics committee checks this before the research starts.

Further information

What if I have a complaint?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. If you have any concerns about any aspect of this study you should speak to your study doctor who will do their best to answer your questions.

If you wish to complain or have any concerns about any aspect of the way you have been approached or treated during this study, via the Patient Advice and Liaison Service (PALS) at St Bartholomew's Hospital, Contact Number 020 3465 5919 and Email Address SBHpals.bartshealth@nhs.net; for more details see https://www.bartshealth.nhs.uk/pals.

Where can I find information about the study?

Chief Investigator: Dr. Ajay Gupta	Contact number: 0207 882 2858 Email: ajay.gupta@qmul.ac.uk https://www.qmul.ac.uk/whri/clinical-activities/cvctu/ Barts Cardiovascular Clinical Trials Unit (CVCTU)
Investigation Site	William Harvey Clinical Research Centre William Harvey Research Centre Charterhouse Square Queen Mary University of London London EC1M 6BQ
Study Contact:	Contact Number: 020 7882 5664 0800 689 0589
Emergency (Office hours)	0800 689 0589 0207 882 5664
Device Related Issues	0208 243 8698

You will be given a copy of this information sheet and a copy of your signed consent to keep

Centre Number:

Study Number:

Participant Identification Number for this trial:

SCRATCH - HTN

Consent Form – Main Study

Please initial box

1. I confirm that I have read pages 1-12 of this information sheet dated **15 October 2024 (version 8.0)** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from Queen Mary University of London, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers. ☐

5. (If appropriate) I agree to my General Practitioner being informed of my participation in the study. ☐

6. I understand that the information held and maintained by-Barts Health may be used to help contact me or provide information about my health status. ☐

7. I agree to give blood and urine samples in the study. ☐

8. I agree for my blood samples and data to be stored at the Bio-resource for future research, if required and if so decided by the investigators of this study. ☐

9. (If female and appropriate) I understand that during the study, I need to use approved forms of contraception to prevent pregnancy, and if I did get pregnant during the study or within 4 months of my last study contact (at Day112), I must report this to the Study Investigators. ☐

10. I agree to take part in the above study. ☐

Participant Identification Number for this trial:

Name of Participant	Date	Signature
Name of Clinical Researcher/Nurse	Date	Signature
Name of investigator / Physician	Date	Signatiure

Sub-study

If you are interested in participating in the sub-study (mentioned on page 2), you should read this section. If you have any questions, please speak to the nurse or clinician who will talk you through the information sheet.

The sub-study will aim to assess the sympathetic and parasympathetic nervous system, the dysfunction of which has been linked with hypertension. The results of these tests together with the tests from the main study will provide us with objective parameter to document statuses of the resting sympathetic (flight and flight) and resting parasympathetic (calming) activities in an individual together with parameter to document the status of brain-level (central regulatory) mechanisms that help regulate the BP control in the body.

If you participate in the sub-study, you will do the following physiological tests in addition to the main study tests:

- Central BP

This procedure enables noninvasive (painless) measurement of the pressure of the largest artery in the human body – the aorta. During this procedure, we will attach several electrodes on to your chest and a probe to wrist, neck and top of your leg. We will do the Central BP assessment at visit 2 (baseline visit) and visit 5 (End of Trial visit).

- Autonomic Target-organs Neurophysiological tests (ATONT assessment)

ATONT assessment enables us to assess the autonomic nervous system function. During this assessment we measure your BP during each heartbeat, time within each heartbeat, breathing rates, oxygen levels in skin tissue on a continual real-time basis whilst you are asked to do simple tasks such as stand up, deep breathing, blowing air out, etc.

You will be asked to complete the ATONT assessment at visit 2 (baseline visit) and visit 5 (End of Trial Visit).

- We analyse your blood samples further to measure plasma acetylcholine, extracellular vesicles and lipid mediators, which will help as understand how your nervous system function is affected by the treatment.

In order to complete all assessments and allow time for collation and review of all assessments, we may have to split Visit 2 in two parts (meaning that you may have to come to the clinic 6 times in total).

Study Number:

Participant Identification Number for this trial:

SCRATCH - HTN

Consent Form – Sub-Study

Please initial box

1. I confirm that I have read pages 1-15 of this the information sheet dated **15 October 2024** (version 8.0) for the above sub-study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I agree to take part in the above sub-study and perform the additional assessments for the sub-study as described on page 15 of this sheet. ☐

3. I confirm that all the Informed Consent points (1-10), I initialled for the main study, are applicable to the sub-study also. ☐

Name of Participant	Date	Signature
Name of Clinical Researcher/Nurse	Date	Signature
Name of investigator/physician	Date	Signature