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A Multicentre Randomised Controlled Study: Does Neuromuscular Electrical Stimulation Improve the Absolute Walking Distance in Patients with Intermittent Claudication (NESIC) compared to best available treatment?

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Disclaimer

The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NHS, NIHR or the Department of Health.

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PATIENT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT

You have been invited to take part in a research study called NESIC. Before you decide whether to accept, we would like to explain why the research is being done and what it will involve.

Please read this information carefully, and discuss it with others if you wish. Ask us if anything is unclear, or if you would like more information.

- *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 the conduct of the study.*

Please take your time to decide whether or not you wish to take part.

Thank you for reading this information sheet.

Part 1

What is the purpose of the study?

Patients with intermittent claudication (IC) are known to have poor circulation in their legs and feet leading to complications such as painful legs while walking or resting. A new device has become available to improve circulation in the legs, and the aim of this study is to look at its effect on people with limited walking distance.

Why have I been chosen?

You have been invited to consider this study because you are a patient with intermittent claudication and have a problem with blood circulation in your legs. We hope that about 192 people like you from across the UK will take part in this study.

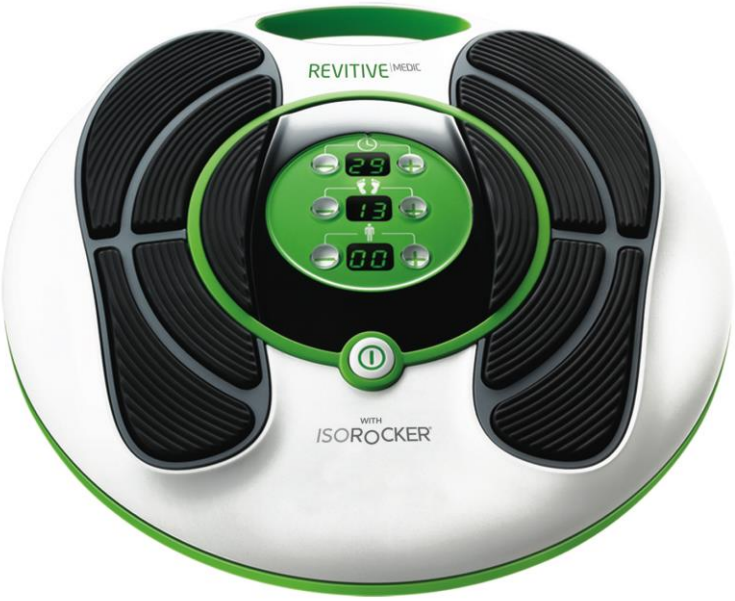
Do I have to take part?

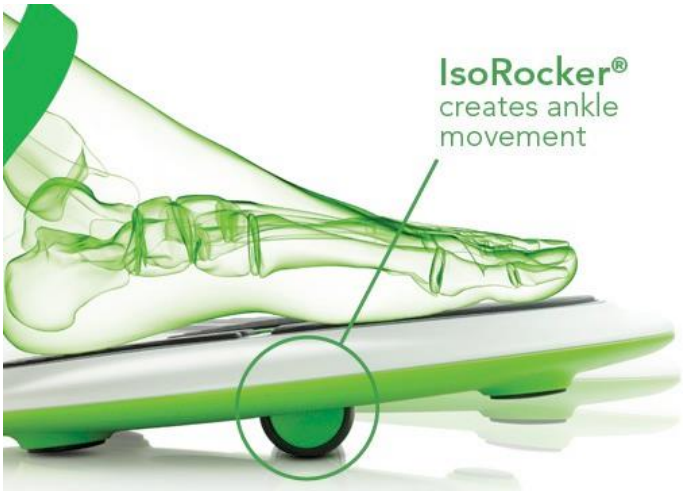
No, participation in this study is entirely voluntary. If you do decide to take part you will be given this information sheet to keep. You will be asked to sign a consent form, but you are still free to withdraw at any time and without giving a reason. If you decide not to take part in the study, your doctor will be happy to talk through how he/she will treat you outside of the study. You do not have to give a reason for not taking part and your treatment and care will not be affected in any way. By taking part in this study you are helping us to develop a new treatment for people with claudication.

Tell me more about the device

The device is called Revitive® IX and is made by Actegy® Health LTD. The Revitive® IX device activates your leg muscles by applying proven Electrical Muscle Stimulation (EMS) to the soles of your feet through two large foot pads. This EMS makes the foot and calf muscles contract and relax to create a pumping action. The IsoRocker mechanism allows the Revitive® IX to gently ‘rock’ back and forth creating involuntary ankle movement to replicate heel toe raises. Consequently the blood immediately moves through the arteries in your legs and back to your heart, improving circulation. The device is CE marked which means it has passed health and safety tests and is available to buy online or over the counter from a pharmacist and be used as a circulation booster. It does not have a CE marking showing any benefit for patients with

Intermittent Claudication but it is safe to use in this patient group. The device is not noisy and therefore can easily be used while doing your normal activities like watching television or reading.





What will happen to me if I take part?

If you choose to be involved in the research, your participation will last for 12 months from trial entry. The following section tells you more about each visit you will be expected to attend.

There are no restrictions on your activity when you are taking part in this study. You will continue with any other medical care or treatments, such as taking regular medication, as you would normally do. There are no limitations on you seeking other medical advice, if you need to, whilst you are taking part in this study.

Your first visit

If you decide to participate in the study, the following steps will be taken at your first visit (often referred to as the screening/baseline visit) which will last approximately 1.5 hours:

- You will first sign the consent form to confirm that you would like to be included (you will be given a copy of this).
- Some information about your medical history and current medical condition will be collected to check that you are able to take part and will include the completion of a claudication questionnaire to evaluate the level of claudication.
- If you are female and of childbearing age, a urine pregnancy test will be performed to confirm that you are not pregnant. This sample will be destroyed immediately after testing.

If the research team confirm that you are able to take part in the study, a computer programme will randomly select whether you will receive either ‘standard care’ or ‘standard care plus the device’. There is an equal chance of either treatment being the one you will receive. Neither your doctor nor you will choose which treatment you receive. In this way, a fair comparison between the two groups can be made.

You will have your blood pressure and pulse rate measured. Other measurements that will be recorded include height, weight and blood pressure measurements at the arm and ankle.

An initial treadmill test will be done to establish the distance at which you experience the onset of your symptoms.

An ultrasound scan of your upper leg blood circulation will be undertaken to measure your blood flow. The ultrasound technician will spread a gel over the area being tested which helps the sound waves get into your tissues. A wand, called a transducer, is moved over the area being tested and sends out the sound waves. A computer measures how the sound waves reflect back, and changes the sound waves into pictures. The Doppler creates a "swishing" sound, which is the sound of your blood moving through the arteries and veins.
You will also have your blood flow measured by a machine called a laser Doppler. The laser optical probes will be positioned on your hand and foot using adhesive pads and measurements taken. Neither the ultrasound or doppler will be painful.

At this visit you will also be also asked to complete three health questionnaires about your quality of life so we can collect information about your health throughout the study. These are called the (The EQ-5D-5L, the SF-36 and the Intermittent Claudication Questionnaire). In some instances we might send you the health questionnaires by mail or obtain them over the telephone.

Standard care arm

Your treatment plan will be the same as those who decide not to enter the trial and will involve optimisation of your cardiovascular medications, smoking cessation advice, regular exercise advice and enrolment onto a supervised exercise programme. The supervised exercise programme differs slightly from hospital to hospital but usually involves a total of 30 minutes of physical activity made up of rotating through various low impact exercises (treadmill walking, steps, stretching etc.) under the supervision of a health care professional e.g. physiotherapist or nurse once or more times a week for around 3 months.

Device arm

If you have been allocated to the group that will receive the device, you will receive the standard care as detailed above but you will also receive training on how to use the device and be given a user manual to take home with you.

- You will be asked to place both your feet on the footpads of the device through which electrical muscle stimulation will be delivered at intensity sufficient to create lower limb muscle contractions. This intensity level may need to be increased over time as you get used to the stimulation. It is important you stay hydrated, as this aids the device therapy.
- Ensure the IsoRocker is enabled. This allows the feet on the device to naturally rock back and forward increasing mobility in the ankle.
- During this time and for a few minutes afterwards, ultrasound and laser Doppler measurement of the circulation in your legs will be taken.
- At the end of this visit, you will be advised to use the device for a minimum of 30 minutes per day for a total period of 3 months, or if diagnosed with diabetes, you will be advised to use the device for a minimum of two (2) x 30 minute sessions per day for a total period of 3 months.
- You will be given a device diary to record when you have been using the device. The device may also come with a data logger attached which measures when the device is switched on, this will work automatically and you do not need to do anything with this.
- All participants will be given another diary to complete whenever you see a doctor or nurse so we can collect the costs associated with the condition and also an exercise diary to complete when you attend the supervised exercise programme and do your own exercise.

We will then invite you back to the hospital at 3 months (the end of the treatment period), 6 months and 12 months for repeated measures of the above tests in order to answer our research questions (the duplex will only be performed at baseline and 3 months).

During the first 3 months

If allocated the device you will be advised to use the device daily for a minimum of 30 minutes for a total period of 3 months thereafter. If you have been diagnosed with diabetes, you will be advised to use the device daily for a minimum of two (2) x 30minute sessions per day. You will be given a device diary to record when you have been using the device. You will also attend the supervised exercise programme as directed by your doctor or physiotherapist and record these visits in your diary. You will also be encouraged to do at least 30 minutes of exercise each day in addition to these classes.

If allocated to the standard care alone arm you will attend the supervised exercise programme as directed by your doctor or physiotherapist and record these visits in your diary. You will also be encouraged to do at least 30 minutes of exercise each day in addition to these classes.

We will send you weekly text messages to remind you to complete your diaries and exercises.

3 Month follow-up

Following this 3 month study period, you will be invited for a session of measurements similar to the first session which will also last approximately 1.5 hours.

At this time, you will be asked to complete the same pack of quality of life questionnaires that you answered at the first visit. If you have been allocated to use the device we will ask you to complete an additional questionnaire to collect information on the ease of use. We will also ask you questions about any adverse events you may have experienced related to the device. At the end of the 3 month visit if you have been allocated a device you are free to continue using it after the 3 month treatment period if you wish.

6 Month follow-up

At 6 months you will be invited for a session of measurements similar to the first session but without the duplex and will last about an hour. You will be asked to complete the

same pack of quality of life questionnaires again. If you were allocated to the device will also ask you questions about any adverse events you may have experienced related to the device.

12 Month follow-up

At 12 months you will be invited for a final session of measurements similar to the last session which will also last approximately 1 hour and will conclude your study participation. You will be asked to complete the same pack of quality of life questionnaires again. If you were allocated to the device will also ask you questions about any adverse events you may have experienced related to the device.

What is the standard treatment?

If you decide not to take part in the trial, in most hospitals you will be offered the standard care for intermittent claudication which involves optimisation of your cardiovascular medications, smoking cessation advice, regular exercise advice and enrolment onto supervised exercise programme. This is the same as the standard care arm of the trial.

What are the alternative forms of treatment?

Most people with intermittent claudication can manage their pain with exercise and treatments that reduce the risk of other cardiovascular problems. An alternative treatment for intermittent claudication is 'revascularisation' (a procedure on the arteries that increase the amount of blood that can get to your legs). People are usually offered revascularisation for specific reasons determined by their doctor, and if you require this you would not be eligible to participate in this study.

Unwanted effects of treatment

You should not join the study if you have an implantable pacemaker or defibrillator device or an acute deep veins thrombosis (DVT). If you have previously had a DVT your doctor will decide if you are eligible to take part.

Pregnancy

It is possible that if the device is used by a pregnant woman it will harm the unborn child. Pregnant women must not therefore take part in this study; neither should women who plan to become pregnant during the study. Women who could become pregnant will be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy and must use an effective contraceptive during the course of this study. Contraceptive methods that can achieve a failure rate of less than 1% per year and when used consistently and correctly are considered as highly effective birth control methods. These include:

- ✓ combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- ✓ progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- ✓ intrauterine device (IUD)
- ✓ intrauterine hormone-releasing system (IUS)
- ✓ bilateral tubal occlusion
- ✓ vasectomised partner
- ✓ sexual abstinence- if this is a compatible lifestyle choice

Any woman who finds that she has become pregnant while taking part in the study should immediately tell her research doctor. The research team may request to collect additional follow up information in such circumstances.

You may be withdrawn from the study if the doctor feels it is best for you not to participate or if you do not comply with the requirements of the study. If during the health screening tests any abnormal results are found, you will be immediately referred for clinical review as appropriate. If you feel any discomfort or distress during the study you

must say so immediately and we will stop straight away. If for any reason during the study and you do not wish to continue, than we will stop the tests immediately.

All of the previous work using the Revitive® IX device has demonstrated it to be safe. When the Revitive® IX device is applying an electrical stimulation, you will feel some muscle twitching, contracting and maybe tingling in your lower legs. This is the normal sensation of Electrical Muscle Stimulation. There are very few risks or dangers involved in using this type of equipment. The Revitive® IX user manual details give more information on how to use the device and any safety precautions that should be taken.

How is my condition monitored?

Participating in this study will not significantly affect how your condition is monitored or any other treatment you receive for it although you would be reviewed in clinic more regularly than you would be outside the study.

What are the possible disadvantages and risks of taking part?

The device has been through the national testing process and is safe to use for healthy individuals to improve circulation in the legs. The aim of this study is to look at its effect on people with Intermittent Claudication as the device has not been tested in these individuals. However, we do not anticipate any additional risks for this patient group.

Activation of the device causes small impulses to travel through the skin to make your foot and calf twitch. It may be an odd sensation but should not hurt. You may experience potential discomfort but, the device has variable intensity settings which you can adjust to a comfortable level of stimulation. There are 99 levels of intensity which can be adjusted for your comfort.

Muscle fatigue and or sleeplessness can occur if the device is used on too high an intensity setting, for too long or too many times during the day. The device instruction manual instructs the user to avoid these risks by starting conservatively and increasing the treatments gradually.

The device should NOT be used by the following individuals:

- women in the first trimester of pregnancy
- Patients fitted with an electronic implantable devices e.g. pacemakers or Automatic Implantable Cardioverter Defibrillator (AICD)
- Patients with existing Deep Vein Thrombosis.

What are the possible benefits of taking part?

We know from previous studies that the Revitive® IX device increases blood flow in healthy people. We expect it to do the same for patients with intermittent claudication. If you have intermittent claudication we expect there to be a direct benefit to you. You will not get paid for participating in this study.

What if I do not want to take part?

If you do not wish to take part in the study your doctor or nurse will offer you the standard treatment for intermittent claudication. In most hospitals you will usually be offered blood thinners.

What happens when the research study stops?

At the end of the study period (12 months from your baseline appointment), you will be offered a device for free if you would like one regardless of whether you were allocated the device during the study or not. At the end of the 12 months you will revert back to standard care for your condition.

The information from this study will be used to decide if the Revitive® IX offers any additional benefit to patients with intermittent claudication. In addition, the research team will also use the information collected to compare the safety and cost of the device and standard care.

What if something goes wrong?

A group of independent researchers (called the Data Monitoring Committee) will closely monitor the study. If there are any problems then they will be detected as soon as possible so that the study can be changed or stopped if necessary.

Will my taking part be kept confidential?

If you decide to participate, the information collected about you will be handled strictly in accordance with the consent that you have given and also the 1998 Data Protection Act. Please refer to Part 2 for further details.

This completes Part 1 of the Information Sheet. If the Information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

What if relevant new information becomes available?

Sometimes during the course of a research project, new information becomes available about a device that is being studied. If this happens, your research doctor will tell you about it and will 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.

What will happen if I don't want to carry on with the study?

You can decide to leave the study at any time. You do not need to give a reason.
If you leave the study before your treatment, then your doctor will discuss with you what type of treatment he will use outside the study. If you decide to leave the study after the treatment, any data collected up until that time will remain on file and will be included in the final study analysis and follow up information will continue to be collected from your medical records.

If you decide to leave the study and do not wish for any further data to be collected about you, you should inform your clinical care team of this in order that no further follow up information is collected from your medical records. In line with Good Clinical Practice guidelines, at the end of the study, your data will be securely archived. In this study, data will be archived for a minimum of 10 years after which arrangements for confidential destruction will be made.

What if something goes wrong?

Imperial College London holds insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (Insert name and contact details). The normal National Health Service complaints mechanisms are also available to you. If you are not satisfied with the response, you may contact your local Patient Advice and Liaison Service (PALS) which offers confidential advice, support and information on health-related matters (insert contact details). You may also contact the Imperial AHSC Joint Research Compliance Office (Room 215, Medical School Building, St. Marys Campus, Norfolk Place, London W2 1PG. Tel: 0207 594 9459).

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

With your permission, your data will be entered onto a secure database held at Imperial College London, in accordance with the 1998 Data Protection Act. Your relevant medical records may be inspected by authorised individuals from the research team, NHS or Imperial College London (the study Sponsor). They may also be looked at by the relevant regulatory authorities to check that the study is being carried out correctly.

Anonymous data may also be linked with appropriate national databases, including Hospital Episode Statistics (HES), and the National Vascular Database as well as for longer term follow-up in the event the trial is extended.

Your mobile phone number will be entered into a secure database hosted by a company called The 3rd Degree who will send you weekly text message reminders. This company is regularly used by the NHS and will keep your number confidential. The company that make the device (Actegy Health Ltd) will only have access to the anonymised results and safety information. The Health Economist is based at the University of Granada and therefore your pseudonymised data will be transferred there so they can determine the cost and effect on your quality of life that the two treatments may have.

Involvement of the General Practitioner (GP) / Family Doctor:

With your permission, your GP and other doctors involved in your clinical care will be kept informed of your participation in the study, but otherwise all information about you and your treatment will remain confidential. We may contact your GP to obtain information about your health status if we cannot reach you.

What will happen if I lose mental capacity during the study period?

This is expected to be a very rare occurrence. If this did occur your doctor or carer will determine whether you should be withdrawn from the study. If you are withdrawn, any identifiable data already collected with consent will be retained and may be analysed, but no further data will be collected or any other research procedures carried out on or in relation to you.

What will happen to the results of the research study?

When the study is complete, we plan to inform patients of the results of the study by letter, email, newsletter, social media or publication on the trial website. We may ask patients if there are any other methods they would prefer. The results will be presented at conferences and published in a medical journal. No individual participants will be identified.

Who has organised, reviewed and funded the research and who will be supervising it?

This research is funded by the Efficacy and Mechanism Evaluation (EME) Programme, a Medical Research Council (MRC) and National Institute for Health Research (NIHR)

partnership. The Sponsor of this study (Imperial College London) will pay your hospital to cover the costs of your participation in this study. You are able to claim the travel costs (e.g. bus / train / tube fare or parking costs and petrol) of your hospital visits. Please speak to the study nurse about how to make this claim. The research is being co-ordinated by Imperial College London, who have overall responsibility for coordination of the study. The research has been reviewed by the National Institute for Health Research, representatives from all of the participating hospitals and organisations, and an independent National Research Ethics Committee, and the Health Research Authority (HRA).

Contact Details

If you have any further questions about your treatment, please discuss them with your doctor. You may also find it helpful to contact the research nurse on XXXXXX.

If you would like further information about clinical research, the UK Clinical Research Collaboration (a partnership of organisations working together on clinical research in the UK) has published a booklet entitled 'Understanding Clinical Trials'. Contact UKCRC: website: http://www.ukcrc.org/wp-content/uploads/2014/03/iCT_leaflet.pdf

THANK YOU FOR READING THIS INFORMATION SHEET

NESIC STUDY- AN OVERVIEW

<table>
<tr><td>1ST study visit (about 1.5 hours)</td><td>If you agree to take part:
The nurse will confirm you are eligible to take part
You will sign a consent form
You will take a pregnancy test (if you are female)</td><td>You will complete four questionnaires, two about your health in general called:
SF-36
EQ-5D-5L
And two about your leg pain, called:
ICQ
ECQ</td><td>The doctor or nurse will record:
Your blood pressure, height and weight
How far you can walk on a treadmill
Results from an ultrasound scan on your legs
Laser doppler measurements from your legs
The pulses in your legs</td><td>The nurse will ask you questions about your:
Medical history
Medication
Lifestyle</td><td>A computer will randomly assign you to receive either:
Supervised exercise therapy at the hospital
OR
The medical device to take home and supervised exercise therapy at the hospital</td></tr>
<tr><td>0-3 months</td><td colspan="2">If you were allocated to Supervised Exercise Therapy only:
The physiotherapist will book appointments for you to attend classes. Please also complete at least 30 minutes of other exercise every day and record in your exercise diary</td><td colspan="3">If you were allocated to Supervised Exercise Therapy and the device:
The physiotherapist will book appointments for you to attend classes AND you will take the device home and use it for 30 minutes per day and record in your exercise diary. If you have been diagnosed with diabetes, please use the device for a minimum of two (2) x 30 minutes per day and record in your device diary.</td></tr>
<tr><td>3 month hospital visit (about 1.5 hours)</td><td>If you used a device you will complete questionnaires about:
Your experience of using the device at home
How much you used the device</td><td rowspan="2">The doctor or nurse will record:
Your blood pressure
How far you can walk on a treadmill
Laser doppler measurements from your legs
The pulses in your legs
Results from an ultrasound scan on your legs</td><td rowspan="2">The nurse will ask you questions about:
Your use of health services since your last visit</td><td rowspan="2">You will complete three questionnaires, two about your health in general called:
SF-36
EQ-5D-5L
And one about your leg pain, called:
ICQ</td></tr>
<tr><td>6 month and 12 month hospital visit (about 1 hour)</td><td></td></tr>
</table>

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Site ID:	Initials:
Participant Trial ID:	Principal Investigator Name:

A Multicentre Randomised Controlled Study: Does Neuromuscular Electrical Stimulation Improve the Absolute Walking Distance in Patients with Intermittent Claudication (NESIC) compared to best available treatment?

PATIENT CONSENT FORM

Please initial each box

1. I confirm that I have read and understand the information sheet dated 19/11/2018 (Version 4.0) for the above study and have had the opportunity to ask questions which have been answered fully. ☐

2. I understand that my participation is voluntary and that I am free to leave the study at any time without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical records may be looked at by authorised individuals from the research team, from regulatory bodies, from the study Sponsor, or from the NHS Trust in order to check that the study is being carried out correctly. I give permission, provided that strict confidentiality is maintained, for these bodies to have access to my medical records for the above study. ☐

4. I understand that even if I decide to leave the above trial, the data collected about me will be used in analysing the results of the study. I understand that my identity will remain anonymous. ☐

5. I agree to allow any information or results relating to the safety and monitoring of this study to be used for healthcare and/or medical research purposes. I understand that my identity will remain anonymous. ☐

6. I agree to the anonymised imaging and reports from my duplex ultrasound and laser Doppler being sent to and stored at Imperial College London. I understand that I will not be identifiable from the images. ☐

7. I understand that my anonymised data will be transferred to the University Of Granada for the analysis. ☐

8. I understand that my personal data will be stored securely in facilities at Imperial College London for a minimum of 10 years following completion of the study. ☐

9. I understand that my mobile phone number will be stored securely by the 3rd Degree and used to send weekly text message reminders ☐

10. I agree that my data may be linked with appropriate national databases, including Hospital Episode Statistics (HES), and the National Vascular Database as well as for longer term follow-up in the event the trial is extended ☐

11. I agree to my GP, or any other doctor treating me, being notified of my participation in this study and that they may be contacted for information about my health status ☐

12. If during the study my clinical care team determine that I have lost capacity to provide informed consent, I will be withdrawn from the study and any identifiable data collected with consent would be retained and used in the study. ☐

13. I agree to be contacted in the future with regards to this study, should the study be extended. ☐

14. I agree for a copy of this consent form to be held by Imperial College London in a secure facility. ☐

15. I agree to take part in the NESIC study. ☐

Full Name of Participant	Date	Signature

Name of Person Taking Consent	Date	Signature

(1 copy for participant; 1 copy for the patient's medical notes, 1 copy for the site file)