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MINOcycline in the Treatment of Atheroma that are Unstable or Ruptured Study (MINOTAUR)

Participant Information Sheet

You have been asked to take part in a clinical research study. Before you decide whether or not to take part, it is important for you to know why the research is being done and what it involves. Please take time to read carefully the following information about the study before you make your decision and ask us if there is anything that is unclear or if you would like more information. Please feel free to discuss it if you wish with friends, relatives or your personal doctor (i.e. general practitioner). Take time to decide whether or not you wish to take part.

If you are satisfied with this information and wish to take part in this study, you will be asked to sign the consent form; the supervising doctor will also sign it. You are still free to change your mind about taking part even after you have signed the consent form.

The information sheet is in two parts:

- Part 1 tells you why the study is being carried out and what will happen if you take part.
- Part 2 gives you more details about how the study is carried out.

PART 1

What is the purpose of this study?
The carotid arteries are the main blood vessels supplying blood to the brain and are found on both sides of the neck. The narrowing of these arteries is an important cause of stroke. This is commonly caused by fatty deposits in the lining of the blood vessels, called 'atheroma' or 'plaques,' otherwise described as 'furring up' of the arteries. Typically these deposits build up over a person's lifetime and when they reach a significant size can limit the blood supply to the brain. An 'ischaemic stroke,' the most common type of stroke, occurs when insufficient blood supply reaches the brain, causing a part of it to die. This usually occurs when the plaque ruptures, causing a blood clot to form over the area that may break off and block the blood supply to the brain.

Work done by our group has found that the shell overlying the plaque can become damaged by small deposits of calcium ('microcalcification'), which makes the plaque more likely to rupture. To date, there is no drug treatment for reversing this microcalcification. However, recent research has shown a drug called minocycline reduced microcalcification developing in rats. Minocycline is an antibiotic used in routine clinical practice, typically to treat acne.

This study aims to test whether minocycline reduces microcalcification in humans. We can measure the amount of microcalcification in your arteries using a specialist scan called Positron Emission Tomography (PET), which uses radioactive 'tags' that show areas of microcalcification. This tag, called NaF (sodium fluoride), shows areas of microcalcification. The PET scanner is located in the Radiology Department in Addenbrooke's Hospital and is similar to the scan that you will have had at the time of your stroke.

If you chose to take part, you would have two PET scans and two blood samples in addition to your routine clinical care (one pair of a scan and blood sample in the first two weeks after your stroke and the second pair after twelve weeks). All participants will be prescribed the standard medical therapy for reducing further strokes (as per their medical team's guidance), and half the individuals will receive minocycline. The dose of minocycline used in this study is the same as that used in routine clinical care.

Why have I been invited?
You have been chosen because you have been found to have a degree of 'furring up' (plaque) in the carotid or vertebral arteries during tests performed after your recent stroke. If you wish to take part *and* you meet all of the requirements, you will be considered for the study.

Do I have to take part?
No. You should decide for yourself whether you wish to take part or not. We will describe the study and go through this information sheet with you. If you wish to take part we will ask you to sign a consent form to show you have agreed to take part. If you decide to take part, you can withdraw from the study at any time even if you have signed the form. You will not have to state why you have made that decision and it will in no way affect your future care.

What are the possible benefits of taking part?
Any results that may be useful in making decisions about your care will be passed on to the doctors looking after you. There may be **no** direct benefit for you in taking part, but the results of this study will help our understanding of the processes involved in stroke and may help to improve the treatment of the disease in the future.

Will taking part interfere with my treatment?
No. The scans will be arranged at your convenience and any treatment you need will take priority.

What will happen to me if I take part?
If you decide to take part, we will ask you to come on *two occasions* (the first of which may be during your admission) to Addenbrooke's Hospital. You will be reimbursed for any travel expenses incurred in attending the scan sessions.

At the PET scan, a cannula (a thin plastic tube similar to the one you will have had during your hospital admission) will be inserted into a vein in your arm through which the tracer would be injected. A blood sample will be taken through this cannula to test for markers linked with microcalcification. We would then aim to do the scan 60 minutes after the injection of the NaF tracer. You will be asked to lie with your neck in a PET/CT machine (which is shaped like a large doughnut). The PET/CT scanner can detect the tracer, identifying where it is in the blood vessels of your neck, and how much is present. The technique is so sensitive that only a very tiny amount of the radioactive tracer is required. During the scan, you will be asked to lie flat on a bed on your back. Your neck will be supported by a stiff collar to limit movement, which can interfere with the images the scan produces. Once you are settled comfortably, we will ask you to stay in the same position for the time it takes to do the scan *(approximately 20 minutes)*. During the PET/CT scan, a detailed CT scan of the arteries in your neck will also be performed with contrast dye injected through the cannula in your arm. You are strongly advised not to go to work on the day of your scan. We also recommend that you don't have close contact with pregnant women or young children for 8 hours after the scans, as the tracer takes a little while to leave your body (it comes out through the urine). You are encouraged to drink plenty of fluids of any type as this will help flush the tracer through your kidneys.

Overall, the visits will last approximately two hours. You will be accompanied by one of the research team. You are welcome to bring someone with you who can be present at all times except from the injection of the tracer to the completion of the scan.

All participants in the study will receive standard medical care following their stroke, with half of participants randomly assigned to receive the minocycline drug in addition to the standard medical care. Therefore, it is not guaranteed you will receive the drug, but we would still perform the scans and clinical review (as above).

The entire research project will be carried out over two years and it is expected that you will be involved for a maximum of 12 weeks (from signing the consent form to the second PET scan). At the end of this 12 week period, participants taking minocycline will then stop this medication.

There are no specific additional things you need to do before any of the scans.

Smoking	You can participate in this study if you are a smoker. However, you will not be allowed to smoke whilst in the hospital.

Summary of participation:

Visit 1 (within 14 days of your stroke)	Combined PET/CT with angiogram.
Visit 2 (12 weeks after visit 1)	Combined PET/CT with angiogram.

What are the possible disadvantages and risks of taking part?
The PET/CT scans use radioactive tracers which are safe and have been used in human studies without any serious side effects, but do involve some radiation. The tracers break down very quickly and disappear from the body within a few hours through the urine. There is also a small radiation dose from the CT part of the scan. The total radiation dose in the study is comparable to roughly 5 years of exposure to natural background radiation in the UK. This radiation dose carries a risk of cancer of 0.06% (equivalent to roughly 1 in 2000 people), but this should be compared to the natural lifetime risk of cancer of about 1 in 2 over an average person's lifetime.

Although it is extremely unlikely that an allergic reaction or other side effect will occur, there are facilities in place within the PET/CT Unit and at the hospital to deal with them. Placing a cannula (small plastic tube) into a vein can cause some discomfort and very occasionally can lead to infection but this is unlikely in the short time it will be in place. Some people can also get bruising at the site where the cannula is inserted. This procedure is performed regularly in the hospital and is generally very safe. The cannula will be inserted 60-90 minutes before the scan and will be removed immediately afterwards.

Minocycline is an antibiotic used in routine clinical care. Like any drug it may cause side-effects, including nausea, vomiting, diarrhoea, skin reactions, or allergic reactions. If you experience any of these, or are concerned about other possible side-effects, then please contact the study team for review. Your other medications will be reviewed at the time of enrolment into the study to ensure that the minocycline does not interact with any medications you are currently taking.

There is a small chance that your scan may show something abnormal that you did not know about. This is because the field of view of the scan includes the tissues and bones in the neck, as well as the blood vessels we are interested in. Examples might include growths in the tissues of the neck, or abnormalities of the bones or blood vessels. There may be areas of PET tracer uptake ("hot spots") that appear abnormal. Though the scans used in this trial may not be the ideal technique for defining exactly what the abnormality might be, you would be given advice about what is found. We would contact you in writing or by telephone if it should appear more urgent. You would be referred to the appropriate specialist for any further investigation required. This may include a further review in an out-patient clinic by one of the stroke team. We would also in this instance strongly recommend that you allow us to inform your General Practitioner (GP) so that he/she is aware of any on-going investigation or treatment you may require. Finding something early in this way has the advantage that treatment can be started early, but, in a small number of cases, it may have an effect on future employment and insurance.

If you have private medical insurance you should check with the company before agreeing to take part in the study to ensure that your participation will not affect your insurance.

Will my taking part in the study be kept confidential?
Yes, all information gathered about you will be handled in confidence. We will not inform anyone of your participation in the study without your consent. The detailed information on this is given in Part 2.

Will my GP be informed?
We will not inform anyone of your involvement in the study without your consent. However, we would recommend allowing us to inform your General Practitioner and any hospital specialist involved in your ongoing care.

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 a decision.

PART 2

What will happen if I don't want to carry on with the study?
You can withdraw from the study at any time. If you withdraw from the study, we will continue to use the data collected before your withdrawal. We would also like your permission to continue to use the information we have gained in the study and invite you to continue your participation in the study if anything was to happen that affected your ability to agree to take part.

What if I am unhappy with things or something goes wrong?
General advice about taking part in research is available on the NHS website (http://www.nhs.uk/Conditions/Clinical-trials/Pages/Introduction.aspx)

If you have general questions about participating in research or are unhappy with your participation in the study, you can also seek advice from the Patient Advice and Liaison Service (PALS) based at Cambridge University Hospitals NHS Foundation Trust. They have an office next to the hospital's main entrance and are also available by telephone (01223 216756) and email on pals@addenbrookes.nhs.uk.

If you have any concerns, questions or complaints regarding the study, please contact **Dr Nicholas Evans or Dr Elizabeth Warburton** or any other member of the team by post, telephone, or e-mail using the contact details below.

Are there compensation arrangements if something goes wrong?
If something goes wrong and you are harmed during the research study, there are no special compensation arrangements. If you are harmed and this is due to someone's negligence, then you may have grounds for a legal action for compensation against Addenbrooke's Hospital (Cambridge University Hospitals NHS Foundation Trust) but you may have to pay your legal costs. The normal NHS complaints mechanisms will still be available to you. We are not covered for non-negligent harm.

Who is organising and funding the research?
This research project is organised by the Stroke Research Group at Cambridge University Hospitals NHS Foundation Trust, under the supervision of Drs Nicholas Evans and Elizabeth Warburton. The Stroke Research Group is part of the Department of Clinical Neurosciences, University of Cambridge. The study is funded by a grant from Varsity Pharmaceuticals.

Who has looked at and approved the study?
All research in the NHS is looked at by an independent Research Ethics Committee to protect your safety, well-being and dignity. This study has been reviewed and given a favourable opinion by the Wales Research Ethics Committee Six. The Administration of Radioactive Substances Advisory Committee has also granted permission for this study to be performed.

How will we use information about you?

We will need to use information from your medical records for this research project. This information will include your NHS number, name, and contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Some of your information may be sent to collaborators working outside of the United Kingdom (including outside of the European Union). They must follow our rules about keeping your information safe.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?
Please visit: https://www.cuh.nhs.uk/corporate-information/about-us/our-responsibilities/looking-after-your-information, or email the Data Protection Officer at: gdpr.enquiries@addenbrookes.nhs.uk

What will happen to the results of the research study?
Imaging data will be kept securely possibly indefinitely in the NHS data archive in accordance with good research practice.

Scientific data generated by data analysis will be kept for the duration of the study until publication and for a maximum of 15 years.

Study results will also be used to write reports and scientific papers which may be published in medical journals but you will not be identified in any report or publication. If you wish, the results of the study can be communicated to you in written form (either a concise summary and/or the scientific paper itself).

Will blood samples need to be taken?
Yes, but these will usually be taken at the same time as the cannula is inserted.

Will video/audio tapes be used?
No.

Contacts for further information

Dr Nicholas Evans **Tel: 01223 216082**

Dr Evans is a Clinical Lecturer and Honorary Specialist Registrar in Stroke Medicine at Addenbrooke's Hospital. He can provide further information regarding the study, and will be present to obtain your signed consent if you decide to participate. He will be present for your visits to the PET/CT Departments.

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Dr Elizabeth Warburton **Tel: 01223 217837**

Dr Warburton is a Consultant Stroke Physician at Addenbrooke's Hospital. She is the Chief Investigator responsible for the study.

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Thank you for considering taking part in this study. If you require any further information, please do not hesitate to contact us, we will be pleased to help you in any way we can.