Participant Information Leaflet

Study Title: The Amiloride Clinical Trial In Optic Neuritis (ACTION)

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. We’d suggest this should take about 30 minutes. Please talk to others about the study if you wish.

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 ask us if there is anything that is not clear and take time to consider whether or not you wish to take part in the research.

What is the purpose of this study?

Optic Neuritis is a condition in which the optic nerve, the nerve which takes signals from the eye to the brain, becomes inflamed. When optic neuritis first happens the vision is reduced in the affected eye, but over the course of weeks to months the vision usually improves back towards normal. In some cases, the recovery of vision can be poor.

You may or may not already have been given steroid treatment from your doctor. This may speed up how quickly your vision improves, but it will make no difference to how much it improves overall. Because it does not affect the overall outcome, not all patients have steroids after optic neuritis. At the moment we do not have a treatment that will prevent the permanent loss of vision that some patients have after optic neuritis.
Because of the inflammation, the cells in the optic nerve lose their ability to control levels of chemicals inside the nerve. We know from laboratory studies that levels of sodium and calcium inside the optic nerve are increased during an episode of optic neuritis. This change in chemicals can damage the nerve cells and the optic nerve may lose some of its cells after an attack of optic neuritis. We know from research studies that the more nerve cells that are lost after optic neuritis, the poorer the recovery of vision.

Recent research has shown that the drug amiloride, which is already in use in the UK and around the world as a diuretic (water tablet), may help the nerve cells to have a steady amount of calcium and sodium inside them. We want to see if giving people amiloride in the early stages of optic neuritis balances the amount of these chemicals inside the nerves, thus helping to stop the nerve from losing cells, and improving recovery of vision from optic neuritis. If amiloride can help protect nerve cells, we would call it a neuroprotective drug.

**Why have I been invited?**

You have recently been diagnosed with acute optic neuritis. We know that most of the nerve cells are lost very early on in an optic neuritis attack. It is likely that the earlier amiloride is given the more effective it will be in saving cells from loss during optic neuritis. Therefore we are asking patients like you to become involved in this study within 28 days of your first symptoms of optic neuritis. We will recruit 46 participants to this trial.

**Why is this study being funded by the Multiple Sclerosis Society?**

Some of the patients in this study have a condition called multiple sclerosis, a condition in which different parts of the nervous system (the brain, eye nerve and spinal cord) can develop further episodes of inflammation.

For some patients, after an episode of optic neuritis they can later go on to develop multiple sclerosis. However, not all patients will develop multiple sclerosis after optic neuritis- some patients will never have any more inflammation in the nervous system again and will not develop multiple sclerosis. From a study following up patients for 15 years after optic neuritis, only about half of all patients with optic neuritis develop multiple sclerosis.

Having an MRI scan of your brain after you have optic neuritis can give you more information about your future risk of developing multiple sclerosis, and having later scans (6 months after the first) can form the basis of diagnosing multiple sclerosis if there has been further evidence of inflammation on the second scan. Some people with optic neuritis are keen to know from their MRI scan how likely they are to go on to develop multiple sclerosis, however
some people with optic neuritis do not find this information helpful. Current guidelines in the UK do not advocate the treatments used in multiple sclerosis for patients who have only had optic neuritis.

We are performing MRI scans as part of this research trial, but we are not looking specifically at the information on the MRI scans about your risk of developing multiple sclerosis or diagnosing multiple sclerosis. Instead, we are using the information in the MRI scans only to help us find out if amiloride protects nerve cells after an episode of optic neuritis. However, if you wish to know this information we can make it available to your ophthalmology or neurology doctor or we (the trial team) can discuss it with you at your 4 week follow up appointment as part of the trial. If you do not want to know this information your doctor will not ask for this information to be taken from your scans and it will not be passed on to your doctor or recorded in your NHS record.

It is important for you to know that in this trial we are not looking to see if amiloride will prevent you from developing multiple sclerosis. We are specifically only trying to find out if amiloride can protect the nerve cells in your eye from damage following optic neuritis.

If you have any questions or concerns, please discuss with the trial team before making your decision on whether you would like the information from your scan passed on to you.

**Do I have to take part?**

It is up to you to decide if you wish to join the study. The doctor you have seen in the clinic has given the trial team your telephone number, and we will call you to ask if you would like to come to meet us to discuss taking part in the trial.

If you decide to meet us we will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This will not affect the standard of care you receive.

**What will happen to me if I take part?**

If you agree to take part in the study and sign the consent form, we will do some further tests that same day. We aim to do as much as we can arrange and that you are able to do at the same visit, but sometimes we have to split the tests across more than one visit. We will try as much as possible to combine or split up the tests to suit your needs. All of the tests and the trial visits take place at the John Radcliffe Hospital in Oxford;

- **We will go through some questions with you about your general health**, any medical problems in the past and any drugs that you are on. We will also ask to record your ethnicity, as this has been shown to be important in optic neuritis.

- **One of the doctors on the trial will examine you** by listening to your chest, feeling your abdomen, and examining your arms and legs.

- **We will also check your blood pressure and pulse, height and weight.**
We will check your vision with 3 different vision charts, some of which have quite faint letters, and we will also check your colour vision.

We will also take some blood samples from you, which will involve putting a small needle into your arm and removing about 20mls (4 teaspoons) of blood.

We will ask you some questions about your quality of life and how this episode of optic neuritis is affecting it.

We will also do some scans of the back of your eyes. These are called an OCT scan and GDx scan. The scans simply involve you looking at a light while we scan your eyes. The scans take about 2 minutes each to do but you will be in the room for about 10-15 minutes while we set up. These scans tell us how thick the layers of nerve cells at the back of the eye are. They will be arranged today or within the next seven days.

You will have a MRI scan of the brain. This will be on the same day as your other tests, or possibly on a separate day soon after. MRI scanning uses magnets to get detailed pictures of the nerve tissue in the brain. Having an MRI scan involves lying flat on a bed in the scanner. The scanner is a fairly narrow tunnel, just slightly wider than your shoulders. The scanner can make some knocking sounds while you are having the scan done, though you will be given ear plugs and ear muffs. Because MRI scanners use magnets and do not use X-rays or radiation they are very safe to have done. The magnet can attract metal objects, so if you have any metal implants inside your body, this is the only situation in which it may not be safe to have a scan done. We want to do an MRI scan because some of the parts of the brain that are important in vision can appear different on MRI scanning after a person has had optic neuritis, and we want to see if amiloride can have an effect on these changes. Each MRI scan will take about an hour to complete.

You will have electrophysiological testing carried out, either on the same day as your other tests, or within 2 weeks of your first appointment. This will be done at the Oxford Eye hospital at the John Radcliffe hospital. This involves you looking at a pattern moving across a screen while we record the electrical activity in the eye and the brain. These are recorded through leads that are attached to the scalp and very thin wire recorders that rest just inside the eyelid. We will use local anaesthetic drops in the eyes so that it is more comfortable for this to be done. These tests will take about 30 minutes. Looking at the electrical signal from the eye and the brain can help to tell us how the nerve is working, and can help us to decide if amiloride is helping or not.

You will start taking the trial drug once enough of these tests have been completed. You will be taking the trial drug as one capsule per day for 5 months. You will be given a diary card to record any problems you experience or additional medication you take during the trial.

- The purpose of the trial is to see if amiloride provides neuroprotection (prevents loss of nerve cells after optic neuritis). To find out, we need to compare active drug (amiloride) with placebo. We put people into groups and give each group either placebo or amiloride. You
will have an equal chance of receiving either amiloride or placebo (this is an identical capsule, but one that does not have any active drug inside it). You will not know which treatment group you are in, and neither will your doctor (although, if your doctor needs to he/she can find out). At the end of the trial, if you wish to know, you will be told which treatment group you were in. The analysed results of all your tests will show us if amiloride is effective. To make sure that groups are the same to start with each patient is put into a group by chance (randomly).

**Later visits**

-4 weeks after your initial appointment we will see you to check your vision, check your diary card to make sure you are not having any problems with the drug and check your blood tests to make sure that they are not being affected by the drug.

-After that we will telephone you at month 3 (3 months after your initial visit) to make sure you are not having any problems. We will also phone you two weeks before month 5 to remind you to stop taking the trial drug.

At month 6 we will repeat all of your blood tests, your vision tests, OCT and GDX scans, MRI scans, electrophysiology tests and repeat the questions about your quality of life.

We will then see you at month 12 (ie roughly a year’s time from now) and we will repeat your OCT and GDx scans, your MRI scan, the quality of life questions and all of your vision tests except colour vision.

Below is a summary table of all the visits and procedures involved in the trial;

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**Expenses and payments**
There is no payment to you for taking part in this trial, but we will pay reasonable travel costs (on presentation of receipts, or standard mileage for cars), for your journey to and from the hospital for your trial visits.

**What will I have to do?**

You will be asked to come to the John Radcliffe Hospital and the Oxford Eye Hospital (both on the same site) to all of the follow up visits (4 visits in addition to your baseline visit, over the course of the next year) and to take the tablet you are prescribed every day for 5 months. We will also provide you with a diary card for you to use to record and problems you are having while you take the drug.

**What are the alternatives for diagnosis or treatment?**

At the moment there is no neuroprotective treatment for optic neuritis. Taking part in this trial would be an extra treatment. Your usual care will not be affected in any way by taking part in this trial or not.

**What are the possible disadvantages and risks of taking part?**

The main risks from the trial come from the side effects of amiloride which are discussed below.

We will ask you to answer a safety questionnaire before going into the MRI scanner, and provided we know all the answers to this, it is a safe test to have done. The scan can be quite noisy while you are inside, but we will provide you with earplugs should you wish. We also have a selection of DVDs in the scanning department that you can watch while you lie back having the scan done.

**What are the side effects of any treatment received when taking part?**

Amiloride is a drug that is already used by doctors in the UK and around the world as a water tablet (diuretic) and given to patients with high blood pressure or too much fluid in their body. It is generally very well tolerated and safe but we know that it does have some side effects.

It is rare for amiloride to cause serious side effects. We know that when given to elderly people, or people with kidney problems, their potassium can become raised, which can cause problems with the heart. However, we know from looking at studies of people like you who are not elderly and who do not have these health problems that high potassium is very unlikely while taking amiloride. We will be testing your potassium level once you have started on the trial to make sure that it is not raised by taking the trial drug. We will take blood tests and ask questions in your medical history about any conditions that can make amiloride more likely to give you raised potassium, like diabetes or any kidney problems.

Like any drug, people can very rarely have an allergic reaction to amiloride.
Amiloride can have other, milder side effects. It can cause headache, stomach upset, nausea (feeling like you are going to be sick) and some upset to your bowel motions. Because it is a water tablet (diuretic) it can also cause you to go to the toilet to pass urine more frequently.

If during the trial you feel that you are having side effects that are bothersome enough to make you not want to take the medication it will be stopped, but we would still want to follow you up with your scans.

Although there is no specific evidence to say that amiloride is harmful in pregnancy or breastfeeding, we do not know that it is definitely safe, so if you are pregnant or planning pregnancy you should not take part in the trial. If you are a woman of childbearing age we would ask you to have a urine pregnancy test at your first visit. As with all research studies, we would recommend that you use two effective methods of contraception for the duration of the trial treatment and for one month after you have finished the treatment (6 months in total). This should take the form of the pill, barrier contraception, an implantable contraceptive device or abstinence. We will also ask that you do not plan pregnancy for the entire duration of the trial (12 months) as you cannot have MRI scans if you are pregnant.

**What are the possible benefits of taking part?**

We cannot promise that amiloride will definitely improve your vision after optic neuritis, but it may help you recover more vision than you otherwise would have done. You should remember though that there is 50% chance you will not receive amiloride. The main benefit of this trial is that we will know if amiloride is a neuroprotective drug, and this information could help thousands of patients in the future.

**What happens after the research study stops?**

After the trial has stopped you will go back to your normal care. For most people with optic neuritis this will mean you don’t need any more hospital visits. You will have already stopped the trial drug (amiloride or the placebo) 5 months into the 12 month time period of the study. If you wish to know, we would be happy to tell you which treatment you were taking (amiloride or placebo) at the end of the study.

**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 suffer will be addressed. The detailed information on this is given in Part 2.

**Will my taking part be kept confidential?**

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

This completes part 1.
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.
Part 2 of the information sheet

What if relevant new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study after new information becomes available, he or she may ask you to sign an updated consent form.

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

You can withdraw from the study at any time. We will still use the information collected up to the point that you withdraw. Any of your blood samples can be destroyed if you wish.

What if something goes wrong?

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact Dr Matt Craner on 01865 231907 or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224 or the head of CTRG, email ctrg@admin.ox.ac.uk

The University has arrangements in place to provide for harm arising from participation in the study for which the University is the Research Sponsor. NHS indemnity operates in respect of any clinical treatment with which you are provided.

Will my taking part in the study be kept confidential?

The study will be conducted in accordance with Data Protection Act (1998). All information collected about you during the study will remain strictly confidential.

The safety blood tests and the eye scan images are done using NHS equipment so are stored in secure NHS laboratory and imaging databases. The safety blood tests are purely for safety so the results of these will not be analysed or used outside of the John Radcliffe hospital NHS laboratory system. The eye scan images will only be stored next to your name and details in the NHS medical notes or in the Oxford Eye hospital image store NHS computers. When the images are analysed as part of the study, this will be in a fully anonymised form.

In the same way, your name and date of birth are held next to the MRI scans you have done in the University of Oxford Centre for the Functional Magnetic Resonance Imaging of the Brain and are kept strictly confidential. When the images are analysed as part of the study or removed from the Centre, this will be in a fully anonymised form.

Apart from the safety blood tests as mentioned above, all of the blood tests, urine and test results we record about you will be held in a fully anonymised form in a secure storage area.
in the West Wing at the John Radcliffe Hospital and on the computer with your MRI images at the Functional Magnetic Resonance Imaging Centre (FMRIB). The anonymised data from the trial will also be held on password protected files on a University computer.

One copy of your non anonymised personal details will be held in a file in the secure storage area. This will link your anonymised code to your personal details and only the trial team will have access to this file.

Responsible members of the University of Oxford, regulatory authorities or the NHS Trust may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations.

Anonymised data collected during the course of the study may be passed on to other organisations which may include commercial organisations and may be sent to associated researchers to countries where the laws don’t protect your privacy to the same extent as the law in the UK. However, the University will take all reasonable steps to protect your privacy, and any data exported remains fully anonymised.

If you agree to take part we will let your general practitioner know you are part of the clinical trial.

What happens if something unexpected is found on your scan?

As we mentioned in part 1 of the information sheet, the MRI scan can give us more information about your risk of developing multiple sclerosis if this is your first episode of optic neuritis. In addition, very occasionally, MRI scans may detect unusual anatomy or pathology. In this case, we would have the scan checked by a clinician and hospital radiologist, in case the abnormality was an artefact of scanning. If the radiologist and clinician felt, however, that the abnormality might be medically important, you would be contacted directly to explain that this was found, and discuss with you if you wish to have a NHS scan arranged. You would be withdrawn from the study, but all information about you kept strictly confidential. Aside from looking for changes on the brain that can indicate your future risk of developing multiple sclerosis, it is important to note that we do not primarily carry out scans for diagnostic purposes, and therefore these scans are not a substitute for a clinical appointment. Rather, our scans are primarily intended for research purposes only.

What will happen to any samples that I give?

Some of your blood samples (at the start and at one month) are to check that amiloride is safe to give, and that you are not having any side effects from it. We will also perform a blood test to rule out a specific kind of optic neuritis that is very rare, but important to rule out (Neuromyelitis optica). These samples will be sent to the laboratory at the John Radcliffe Hospital and will be labelled with your own name. They will be stored as part of your NHS record. If we use any of these blood results in the trial they will be fully anonymised. It is likely that these blood samples have already been taken as part of your routine care for optic neuritis.
neuritis. If that is the case, with your permission, we will use these results wherever possible instead of having to take new samples.

In addition we will also ask your permission to take blood samples and urine samples for research purposes. These samples will be stored in an anonymised form, and will not be labelled with any personally identifying information of yours. If the results from all of the scans that we do on all the participants in the trial show that amiloride can protect nerve cells from being lost after optic neuritis, we would plan to analyse these samples. We know that patients with conditions like optic neuritis that can cause loss of nerve cells, have markers in their blood and urine tests that are raised when nerve cells are damaged and lost. By testing the samples we would know if amiloride can affect these blood marker levels or not.

In addition, we would also like to store your blood samples for future research after this clinical trial has ended. This is because new and existing scientific techniques are improving our understanding of optic neuritis and related conditions all the time, so using your blood and urine samples in research in the future could help improve the overall treatment of this condition.

In order for us to store your blood and urine samples, we will ask you if you will donate these samples, along with the anonymised images from your brain and eye scans as a “gift” to the Nuffield Department of Clinical Neurosciences in University of Oxford. We will only use your samples and images for research in the future in studies that have the appropriate ethical approval. The research may be done locally in Oxford, elsewhere in the UK or abroad, and it may be done by the public or private sector. You will not receive any financial reward from any results of future research that may use your blood samples.

It is important that everyone participating in the trial has the safety blood tests performed in order the make the trial as safe as possible. However you can still take part in the main study without donating your blood and urine samples for research - it is optional.

Will any genetic tests be done?

We do not plan to do any genetic testing specifically as part of this study. However, genetic testing, including DNA sampling can be very useful in helping us to understand why optic neuritis occurs and why it affects different people in different ways. In the future it may also prove useful to look at genetic testing on why different people may get more or less benefit from amiloride. Therefore will we will also ask you if you will donate a blood sample, which will be stored as a gift to the Nuffield Department of Clinical Neurosciences in the University of Oxford, for future research on genetic testing in optic neuritis. As for the other blood samples, the sample will only be used for research that has the appropriate ethical approval, either in the UK or abroad and in the public or private sector.

Again, you do not have to donate a blood sample for genetic testing in order to take part in the rest of the trial - this is optional.

What will happen to the results of the research study?
We intend to publish the results of the study in a medical journal and also present the results at scientific meetings. Each participant will receive a summary of the overall results from all participants in the study. We may use some of the MRI or eye scans (OCT and GDx) images from some of the participants when the study is published in medical journals or presented at medical conferences. If we do this the images will be fully anonymised. No participant identifiable information will be published.

Who is organising and funding this study?

This study is being funded by the Multiple Sclerosis Society of Great Britain and Northern Ireland and is being organised by the Nuffield Department of Clinical Neurosciences in the University of Oxford.

Who has reviewed this study?

The study has been reviewed by the South Central - Oxford Research and Ethics Committee B.

Further information

We would encourage you to ask as many questions as you wish. If you would like to know more details about the trial please ask you study doctor or nurse, who can provide you with the most up to date information about this trial and your condition. If you would like to read any of the research on which this trial is based then please ask your study doctor or nurse and they can provide it for you.

Your Research Fellow

Dr Justin McKee. Tel: 01865 231869 email: justin.mckee@ndcn.ox.ac.uk

The Chief investigator for the ACTION trial

Dr Matt Craner Tel: 01865 231907 email: matthew.craner@ndcn.ox.ac.uk

Further advice

The Association of Research Ethics Committees (AREC) provides general information about research and what it means to participate. Their website can be found on; www.arec.org.uk

We also have printed leaflets from this website in the department and would be happy to provide you with a copy.

If you wish to talk to someone who is not directly related to the trial about potential participation and the nature of the study the trial team will be happy to provide you the opportunity to talk to a qualified MS/Research Nurse. This in addition to the independent sources of information indicated below and considerations highlighted on the AREC leaflets.
Alternatively, you can contact the Multiple Sclerosis Society

The Multiple Sclerosis Society
MS National Centre
372 Edgware Road, London NW2 6ND
Phone: 020 8438 0700

If you have any general questions about taking part in research, then you can contact the NHS patient advice and liaison service (PALS);

Tel: 01865 221473 / 740868 email:PALSJR@ouh.nhs.uk

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