

Dr Christopher Brown
Human Pain Research Group
Clinical Sciences Building
Salford Royal NHS Foundation Trust
Eccles Old Road
Salford
M6 8HD
0161 206 4528

Ethics committee reference number: 09/H1012/44

Participant Information Sheet

Study title: *Interactions between brain opioids and pain in Arthritis*

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?

The study will investigate your brain's response to the pain signals generated by arthritic pain, and whether those signals are related to the way you tolerate and cope with pain. This information will be useful in creating new treatments for chronic pain.

How will I be assessed as suitable for the study?

In order to take part in the study you must be aged 35 or over and have had recurrent or persistent pain in your knee, wrist, or ankle joint for more than 2 weeks due to either Rheumatoid Arthritis or Osteoarthritis. As the study requires several hours of your time over three days, you must be willing to attend each session. It is important that you read and understand this information sheet and sign a consent form to participate in the study. After consenting for the study, if you lose capacity to consent and we have already collected data from you, we will retain and make further use of any identifiable data.

You should *not* take part if you have any of the following:

- Uncontrolled high blood pressure
- Previous stroke
- Previous fits
- Previous brain tumours
- Past organ failure
- History of major psychiatric or personality disorder
- Metal implants of any kind or metal fragments embedded internally or within the eyes.
- Operations or injections to their knees within the last 3 months
- Pregnancy; women able to bear children must undergo a pregnancy test.
- Claustrophobia

Where will the study be held?

The study will be conducted by the Human Pain Research Group at Salford Royal NHS Foundation Trust (SRFT) in Salford, and at the University of Manchester's Wolfson Molecular Imaging Centre (WMIC) in Withington, Manchester. If you agree to take part in the study you will be required to attend SRFT on one occasion and the WMIC on two occasions. The visits will last no longer than 4 hours each time.

Do I have to take part?

Your participation in the study is entirely voluntary. You are free to decline to enter or to withdraw from the study at any time without having to give a reason. Your medical care and rights will not be affected in any way.

What compensation will I receive for taking part?

You will be receive £100 per visit (with a total of 3 visits) in compensation for the time you spend in our research buildings and reimbursed for any travel expenses that you may incur getting to and from the research buildings. If you require transport to take you to the appointments, this can be arranged. If your visits coincide with meal times we will purchase for you a simple meal such as sandwiches and a beverage. All payments will be made upon completion of your involvement in the study.

What will happen to me if I take part in the study?

You will be asked to stop using any pain killing medication before each of the visits. Also, no aspirin or blood thinning agents must be taken during the week before each visit. Prior to your first visit we will discuss with you when you need to stop taking your pain killing medication, as this will vary depending on the type of pain killing medication you use. However you can take paracetamol up to 12 hours before the time of your visit. As soon as you have completed your visit you can start taking your medication again. You will be advised to carry your routine *medication with you whenever you come to the WMIC*. The three visits to our research facilitates required for this study are described below:

Visit 1 for clinical assessment and laboratory tests (at SRFT)

- We will provide a full explanation of this visit and also the scan procedure to take place on your subsequent visits, and will be given an opportunity to ask any questions.
- You will receive a clinical assessment involving measurement of any tender points and a pregnancy test if necessary. We will also give you a number of questionnaires that assess how you normally feel on a day-to-day basis and how you cope with pain.
- During the scanning later in the study, we will need to be able to put your arthritic joint in pain for one of the scans, and out of pain for the other scan. Therefore, at this point in the study we will test if we are able to change the position of your arthritic joints so that you can be either free of pain or experiencing pain. To make your joint(s) feel painful we will either put the joint into an uncomfortable position (e.g. bending or straightening the arm or leg), or we will apply some pressure to the joint using a special device. If we are not able to cause a sufficient level of pain it's possible that you will not be suitable for participating in the scanning sessions, therefore at this point you would not be able to continue with the rest of the study.
- As part of this study we are interested in how well you can tolerate painful sensations. We will therefore measure your pain threshold and maximum tolerance level. To do this we will slowly apply pressure to your thumbnails using a device until you first start to feel an unpleasant sensation. You will be in total control of how much pain you experience, and we will not ask you to tolerate any pain you are not willing to. We will do a similar assessment of your pain threshold with a laser stimulator, which will induce very brief heat sensations on your forearm. We will slowly turn up the heat until it starts to feel mildly unpleasant, and then carry on increasing the heat until it feels moderately painful, at which point the test will stop. Again, you will control how much pain is given to you.

- As part of the study we are also interested in measuring how you attend to pain sensations and other types of sensation. Attention may be related to the brain responses that we will be measuring. We will measure how quickly you can respond (with a button press) to (1) flashes of light, (2) vibrating sensations on your arm or (3) moderately painful heat sensations from the laser.
- Will do a separate attention task while recording the electrical activity of your brain by a procedure known as electroencephalography (EEG). It will involve wearing a stretchy elastic cap containing a number of electrodes that make contact with your scalp. This is a totally safe, non-invasive procedure. In order to make good contact with your scalp, each electrode will be filled with a type of gel. The gel will be in your hair throughout the task, but we have the facilities for you to wash and dry your hair before you leave. *To help obtain good recordings we ask you to have clean hair that day and not to use hair conditioning or styling products such as wax, gel or spray.* For the task, we will deliver the laser sensations on your arm. You will be asked to pay attention to the pain experience by either trying to locate the pain sensation on either the left or right side of your arm, or by thinking about how unpleasant the pain was and rating it on a 0-10 scale. You will also be asked to fill out a questionnaire to rate your mood, since altered emotional states can influence how much pain you feel.

Visits 2 and 3 for brain scanning (at WMIC)

It is important that on both of these visit days you eat the same meal(s) prior to arriving. On visit 2 you will have two scans (in two different types of scanner, described below), but on visit 3 you will just have one scan. Before we begin scanning you will be given more detailed information about the scanning procedure. If you wish, prior to the study you can arrange a visit the scanning department to familiarise yourself with the scanners.

The first scanner is called an MR (magnetic resonance) scanner. During visit 2, we will ask you to lie in the MR scanner for 20mins so that we can take a detailed picture of your brain. However, the scanner can be quite noisy, so we will give you earplugs for your comfort. Also if you suffer from claustrophobia the MR scan may be uncomfortable for you. The scanner works using a large magnet, and therefore for safety you will be asked to remove any pieces of metal from your body.

The second scanner is called a PET (Positron Emission Tomography) scanner. On both visits 2 and 3 you will receive one of these scans. Before each PET scan, we will first apply an EEG cap (in the same way as for visit 1 to SRFT), and you will have a cannula (small plastic tube) inserted into a vein of one arm. This is to allow a small volume of radioactive substance to be injected into your blood stream. The radioactivity eventually reaches the brain where the scanner detects it. This information is then used to study the activity in your brain. A second cannula will be inserted into an artery on the other arm. This will allow us to take periodic samples of your blood during the scanning. An analgesic will be used to numb any pain you might experience from the cannulas. In total, we will take less blood from you than people normally give when donating blood.

After the EEG cap and cannulas are in place, we will then ask you to lie down comfortably in the scanner for about 1 hour and 40 minutes. On one of the visits we will scan your brain while you are experiencing pain caused by the arthritis in one of your joints. The pain will be induced by putting your limb in an uncomfortable position or by applying some pressure to your joint, like we did on visit 1 to SRFT. On the other visit, we will make you comfortable enough that you will not be feeling any pain when lying down at rest. If we cannot achieve this with simple cushioning, we may have to give you an injection of a local anaesthetic (marcaine) and a steroid (kenalog) into your joint. If this is necessary we will have found out in visit 1 to SRFT and prepared you for this possibility. At any point in the study if you experience intolerable pain, scanning will be stopped and you will be able to take your painkillers.

Risks associated with taking part in the study

The total amount of radiation that you receive for the entire study is equivalent to the dose that everyone in Britain receives every 4 years from natural sources. The estimated lifetime risk of fatal cancer associated with the total study dose 7.05mSv is 1 in 2800. Each time you visit the WMIC for a scan you will only receive the radioactive substance once and during the MR scan you receive no radiation. The dose of radiation that you will receive is similar to amount given in previous studies that our group has carried out without any reported negative outcome. After a few hours you will have virtually no radiation in your body as it will have disappeared.

The placement of a cannula in your artery may cause some discomfort, although you will receive a local anaesthetic to the area of insertion. You may notice some soreness and bruising for a day or two. If you have a history of a bleeding disorder or are taking medication to thin your blood, a cannula will not be used. You should also be aware that repeated placements of cannulae in veins or arteries can increase the risk of discomfort or complications. There is a very small chance of complication from this cannula, including bleeding, infection, or blood clot. There is an even more remote risk of cutting off circulation to your hand, which could result in the need for surgical repair or, in rare instances, could result in the loss of use of part or all of the hand. The risk of this occurring in the UK is less than 1%. These complications are rare and usually occur in medically ill patients who have cannulae in their wrists for several days. In contrast, the cannula will remain in your arm for a few hours for this study. When the study is finished, we will take out the cannulae, and put on a dressing.

There is a very small risk of infection due to any injections and cannulas, but the procedures will be done under strict sterile conditions. In the event of any such problems, we will give advice about this and return arrangements will be made before you leave.

After the first visit to SRFT you may experience some reddening of the skin on your arms due to the laser heat pulses, but this should disappear within a few hours to days. There is a risk that you may have some mild soreness of the skin, in which case advice will be given to you about this before you leave. Also, it's possible that this area of skin may have a change in pigmentation, which should return to normal within 4-6 weeks. However, in the 10 years that our group has been using this technique, one case has been brought to our attention where this pigmentation has persisted.

We will be using a pressure-inducing device in some volunteers to stimulate their arthritic pain in the scanner. We will be careful to ensure that the device does not cause pressure that will damage your joint or cause a loss of blood flow. Applying pressure may not be necessary if your pain can be induced by simply changing the position of your limb.

Magnetic resonance (MR) imaging is a very powerful diagnostic technique, and on occasions we have detected abnormalities in the brains of normal volunteers. In case of any abnormalities of clinical significance we will (1) ask a Consultant Radiologist will look at your scans (2) discuss the findings with you and (3) contact your GP. In such cases, you would enter the normal NHS care pathway. Although most people are happy to have problems identified in this way, it may cause distress and lead to some difficulties depending on your personal circumstances. It is important that you are aware of this. It is important for you to know that we cannot estimate precisely when your scans will be assessed, and it may be a substantially long time after the scans took place.

Do I have to take part?

The study is voluntary. If you do decide to take part you will be asked to sign a consent form. This does not mean that you are obliged to complete the research to the end. The study remains voluntary throughout and you are free to withdraw at any time and without giving a reason. If you are currently receiving treatment, a decision to withdraw at any time, or not to take part at all, will not affect the standard of care you receive. All information medical and personal, obtained from this study will be kept strictly confidential and no records bearing your

name will be released to anyone who is not directly involved in this investigation. An Ethics Committee examined and approved this study before anyone was allowed to enrol.

Will my data be confidential?

With your consent, we will inform your GP of your participation in this research study. Wherever possible we will endeavour to keep all information confidential unless a current medical or psychiatric problem is picked up by one of our researchers at any point during the study. If this is the case we do have a duty of care to inform your GP of this and will advise you to speak with a clinician.

Your personal details and responses to questionnaires will be stored on separate secure databases. We assure you that only the researchers involved in the project will have access to the databases and these will be password protected. No information that would identify you personally will be disclosed to anyone outside of the study and any data presented in reports will be in the form of summary scores across a number of people rather than individual responses. NHS Research and Development offices and regulatory inspectors may require access to your clinical notes but only for the purposes of verifying or cross-checking data.

How do I volunteer for this study?

If you wish to volunteer for the study, please contact **Mrs Ann Lenton** or **Dr Christopher Brown** on 0161 2064529 or at Ann.Lenton@manchester.ac.uk to assess whether you are suitable for the study, and to organise a time for you to visit our research laboratory.

If you would like to learn more about the activities of the Human Pain Research Group, please visit our website at www.hop.man.ac.uk/painresearch.

Further information: independent advice and complaint procedure

For access to independent advice regarding your participation in this study, you may contact the Patient Advisory Liaison Service (PALS) service at SRFT (Hope Hospital) also the Patient and Public Involvement in Research Coordinator at SRFT (Hope Hospital). If you wish to make a formal complaint about your treatment during the study, please contact **Professor Anthony Jones** on **0161 206 4566**, at anthony.jones@manchester.ac.uk, or at the postal address at the head of this information sheet.

If you suffer from any injury caused by taking part in this study, the University of Manchester, without legal commitment, should compensate you without you having to prove that it is at fault. This applies in cases where it is likely that such injury results from any procedure carried out in accordance with the protocol for the study.

Magnetic Resonance Scanning – Volunteer Information Sheet

Magnetic Resonance Imaging (MRI) and Spectroscopy (MRS) are very powerful techniques for diagnosing and managing disease. The method can be used to produce either anatomical images from within the body, or to measure certain important chemical compounds in the body. The method is entirely non-invasive and involves no exposure to hazardous radiation (unlike, for example, X-ray imaging). We use MR to research a wide variety of diseases including neurodegenerative disease, cancer, diseases of the bones and joints; and kidney disease. In addition we undertake a large programme of research based on functional MRI (fMRI) to study how the brain processes certain tasks. These investigations use a wide variety of MR techniques and we need normal volunteers in order to evaluate and improve our methods, prior to using them on patients.

MRI is without known hazard and comfortable for most people, with only a few exceptions. People who have electrically, magnetically or mechanically activated implants (such as cardiac pacemakers), or those with metal in their body (such as clips on blood vessels in their brain, or other metal fragments) should not have an MRI because the devices may move or not function properly. However, persons with metal dental fillings may have an MRI. Those who suffer from claustrophobia (fear of enclosed spaces) will probably find an MR study uncomfortable. It is recommended that women who are pregnant do not participate in MRI research. Before you are enrolled in an MRI study, the investigator will perform a thorough screening to be sure that MRI is safe for you.

The MR scanner is a powerful tube-shaped magnet that uses radio waves to create computerized images of the brain and body. Because the magnet is always on, you will be instructed not to bring any metal objects into the magnet suite, as these objects may become airborne and injure someone. The MR scanner magnet will also erase the magnetic strip on credit cards, so you should leave your wallet outside as well.

Because the MRI study involves imaging procedures that are very sensitive to motion, you will be asked to keep as still as possible during the examination. You should expect the study to be noisy, and will be given earplugs to wear. You will be able to talk or listen to the radiographer during the examination, and will have a 'panic button', if you want to stop the scan immediately and be brought out of the magnet.

You will not be able to wear your usual spectacles in the MR scanner. If the study requires that you read or view images and you require vision correction, you should inform the investigator, who can provide you with MR-safe spectacles. It is safe to wear contact lenses in the MR scanner (except colored contacts).

Because MR images may be distorted by metal in the mouth, you may be asked to leave any removable dental devices such as retainers, removable bridges, or dentures outside the magnet suite.

PATIENT DECLARATION – TO BE COMPLETED BEFORE EXAMINATION COMMENCES

Please answer the following confidential questions by circling YES or NO to each one. Some of the items mentioned (marked with *) may interfere with the quality of the pictures obtained during your scan and, in a few cases, can be hazardous to your safety.

If you do not understand any of the questions please ask a member of staff to help you.

- * 1 Do you have a pacemaker or artificial heart valve? YES/NO
- * 2a Do you have a hydrocephalus shunt? YES/NO
- * 2b If so, is it a programmable shunt? YES/NO
- 3 Have you had any operations on your head? YES/NO
- 4 Have you had any surgery to you head or body within the last two months? YES/NO
- 5 Do you have any joint replacements or metal implants? YES/NO
- * 6 Have you EVER had metal in your eyes or worked with metal at high speed, eg: in a machine shop? YES/NO
- 7 Do you have any shrapnel from a war injury? YES/NO
- 8 Do you wear a false limb, calliper or brace? YES/NO
- 9 Do you have dentures, a dental plate or a hearing aid? YES/NO
- 10 Have you suffered from epilepsy or blackouts? YES/NO
- 11 Do you have any ear implants, eg: cochlear? YES/NO

TO BE ANSWERED BY WOMEN OF CHILD BEARING AGE

- a Do you have any intrauterine contraceptive device or coil? YES/NO
- * b Could you be pregnant? YES/NO

I confirm that I have read the above questions and that my answers are correct to the best of my knowledge and belief.

Signed: _____ Date: _____

Witnessed by: _____

Please note - If you have answered YES to any of the questions marked ‘*’ please contact the researcher, prior to your appointment date.