MoNoPly
Models of Nociceptive Plasticity in Chronic Pain

PARTICIPANT INFORMATION SHEET – ARTHRITIS

Title of Project	**Mo**dels of **No**ciceptive **Pl**asticit**y** (**MoNoPly**) in Chronic Pain
Chief Investigator	Dr Christopher Brown

You are being invited to take part in a research study. Before deciding whether to take part, you need to understand why this research is being done and what it involves. Please take time to read the following information carefully and talk to others about the study if you wish. *Please ask us if anything is not clear or if you would like more information.* Please take your time to decide whether or not you wish to take part.

Section 1 tells you the purpose of the study and what will happen to you if you take part.

Section 2 gives you more detailed information about the conduct of the study.

Section 1: Purpose of the study and what will happen

1. What is the purpose of the study?

Chronic pain (i.e. pain lasting more than 3 months) can persist despite the best efforts of doctors. For many patients, treatments such as pain-killing medications simply don't work well, and not everyone can be successfully treated with surgery. This may be because these treatments are not targeting all of the causes of the pain. The feeling of pain depends on complex processes in the nervous system including in the brain. Research has found that some changes can occur in the brain (termed "neuro-plasticity") that are related to chronic pain symptoms, and might even be a cause of why some people develop chronic pain symptoms in the first place. But we don't understand very well what causes these changes or how to treat them.

With this project, we plan to measure the function of the brain as comprehensively as possible, and then to use this information to analyse what aspects of brain function might be contributing to pain. We hope that in the future, the information from this project will be used to find more effective ways of treating chronic pain.

2. Why have I been invited?

You have been invited because you have previously sought medical treatment for chronic pain related to arthritis. We are including participants in this study who are over the age of 18.

3. Do I have to take part?

No – participating in this study is completely voluntary. If you decide to participate you will be asked to sign an Informed Consent Form, however you are still free to change your mind and leave the study at any time (including before or during the study) without needing to give a reason. See Section 2 of this form for further details.

4. Are there any reasons why I cannot take part?

We will discuss with you in detail whether there are any reasons why it would be unsuitable for you to take part in this study. In summary, you will **not** be able to take part if you:

- Are currently or plan to be hospitalised during the period of study.
- Are on excessive dosages of some medications.
- Have a history of serious head injury or brain surgery.
- Have a history of neurological disease.
- Are pregnant, planning to become pregnant, or are breast feeding.
- Have metal in your body, head, or eyes that cannot be removed, such as a cardiac pacemaker, brain clip, shrapnel, metal filings etc. (This only applies if you take part in magnetic resonance (MR) scanning - see below for details).
- Are not able to follow the study procedure for other reasons not identified above.

5. What will happen to me if I take part?

Before we ask you to take part in the study, we will go over the study with you on the phone or in person to ensure that you are eligible and that you are happy to continue.

The study will involve a number of visits (between one and three, all of which are optional), each of which would last between 2 hours and 3 hours (including some breaks for rest or refreshments). After taking part in Visit 1, you are free to decide whether or not to take part in Visit 2 and/or Visit 3, as there is no obligation to do so. On each visit, you will be asked to sign

an Informed Consent Form to say that you are happy to undergo the study procedures - you will be given a copy of this to take away and refer to later.

Here is an overview of the study visits and what will be involved that is specific to each visit. The section following this overview contains more detail on the study procedures (i.e. those we indicate here in underlined *italics*) should you wish to know more.

Visit 1

You will be invited to attend the Clinical Sciences Building at Aintree University Hospital. You will be asked to undergo some tasks that involve recording your brain activity with EEG (*Electroencephalography*) while you feel *electrical sensations* that we will cause on your hand, some of which will feel painful to a level that is tolerable and that you are in control of. In another task, you will watch simple images (shapes) appearing on a computer screen. In both tasks you will also hear *sound sensations* we will provide through some headphones. We will measure how your brain responds to these sensations. We will also ask you to complete a number of questionnaires during this visit, which can be taken away and completed at home if you wish to do so. These questionnaires measure your chronic pain symptoms, your ability to perform normal daily activities, and how well you cope with the pain mentally and physically. We will also ask if you are willing to undergo a brief *tender-point test* involving the research applying pressure to different points on your body.

Visit 2

You will be again be invited to attend the Clinical Sciences Building at Aintree University Hospital, in order to repeat the tests that were done in Visit 1, although only a small subset of the questionnaires need to be completed this second time.

Visit 3

You will be invited to attend the University of Liverpool campus (specifically, the Liverpool Magnetic Resonance Imaging Centre - LiMRIC) where we will take a number of detailed *brain (MRI) scans*. Also during the visit we will cause you to feel some non-painful *vibration sensations* on one finger and *painful pressure sensations* on your thumb, to a level that is tolerable and that you are in control of, so that we can measure how your brain responds to these sensations.

Further detail on study procedures

EEG (Electroencephalography)

The brain produces small amounts of electrical activity which can be detected and recorded at the surface of the scalp using EEG. This is a safe and non-painful procedure and has been used for several decades in clinics as well as in basic research. The activity of the brain involves wearing a number of electrodes with wires attached that rest on your scalp along with a gel solution. Fitting the cap and gel should not be painful, although you might experience some mild discomfort. You will be advised to avoid wearing makeup and hair gel because this makes it more difficult to establish electrical contact between your head and the electrodes.

This is similar to the EEG cap that will go on your head, which will require filling each electrode on the cap with gel. The gel is water-based and can be easily washed out of the hair afterwards. It takes less than half an hour to put on the EEG cap and fill all of the electrodes with gel. The cap will be left on your head for between 1 and 2 hrs while some tests are performed.

Electrical sensations

Before and during the EEG recording, we will conduct tasks in which you will feel touch stimuli applied to one or more fingers using a device that delivers very brief electrical pulses (each one lasting a fraction of a second). This is an entirely safe procedure and very similar to using a TENS machine. Initially, we will spend time adjusting the intensity of the sensation to best suit you. This will involve finding out both your pain threshold (when the sensation is just starting to get mildly painful) as well as the highest intensity level that you are willing to tolerate. After that, when we conduct the tasks, we will know which intensities to deliver that are tolerable for you personally, and you will be in control of whether to tolerate those sensations or have them decreased to a lower intensity. During the tasks, you will feel the touch/pain sensations repeatedly at a fast rate (sometimes faster than once per second) for periods of up to 5 mins at a time. These periods of stimulation will be repeated a number of times if you

are happy to tolerate them for that long. During each period of stimulation, the intensity of the sensation may increase or decrease randomly within your tolerable limits. We will either ask you to just feel the sensations passively while you relax or pay attention to something relaxing, or we will ask you to report to us (e.g. by pressing a button) how you are feeling the intensity of the sensation.

Images on a screen

In another task, we will display brief images of simple shapes (e.g. filled circles) appearing on a computer screen. The task that is very similar to that described above for the electrical touch stimuli, except that you will be asked to press a button when there is a change in the brightness of the image.

Sound sensations

During the above tasks, we will play some simple sounds (beeps) to you through headphones. We want to make sure the loudness is suitable for you (not too quiet and not too loud) and so we will initially spend some time finding volumes of the sounds that will suit you. *Tender-point test*

With your permission, we will perform a brief test lasting about 2 minutes in which the researcher will use their thumb to exert pressure on 18 defined points over your body. Pressure is slowly increased on each point until the tip of the researcher's thumb tip just begins to blanche (whiten), at which point the researcher will ask you whether this is painful.

Brain (MRI) scans

For Visit 3, we first need to make sure it is safe for you to have an MRI scan (for example, it is important that you don't have any metal implants in your body). We will first check this over the phone before you arrive, and again formally on the day.

Firstly, you will be asked to wear a gown (changing rooms are provided) and remove items which are affected by the magnetic field of the scanner (e.g. hearing aids, mobile phones, keys, coins, pens, credit cards - secure lockers are provided). MRI scans are noisy so you will need to wear ear plugs that are provided. To monitor your breathing patterns during the scans, we may provide a respiration belt (a thin elasticated band with a Velcro fastener) that will fit snugly around your abdomen. We may also ask you to wear a finger pulse monitor on your finger or thumb. Neither of these should cause any pain or discomfort.

The scans then involve lying still on a flat surface inside the tube of the scanner for no more than 60 minutes. MRI scanners can be noisy and some people are uncomfortable lying in the small space inside the scanner, so please let us know if you are ever claustrophobic. However, there is a small mirror in front of your face that would give you some view outside. The whole time that you are in the scanner you will be given a buzzer, which you will be able to use at any time if you wish to stop the study. For most of the scans, you can lie with your eyes closed and relax. For one of the scans, we will measure how your brain responds to vibrations and also to pressure sensations on your thumb, but only if you feel this is acceptable and tolerable.

Pressure sensations

During one of the MRI scans (Visit 3), painful and non-painful pressure sensations will be caused to your thumbnail using a device, each one lasting no more than a few seconds. Before the scan begins, we will find two levels of pressure intensity that are tolerable for you: one will be a “low” intensity (non-painful) and the other a “high” intensity that is painful but below the level that you tell us is the maximum you are willing to tolerate. The scan that involves these pressure sensations will take no longer than 20 minutes and you will not feel more than 30 of the “high” sensations during that time. During the scan, we will ask you to indicate how intense the sensation is, and this will allow us to decrease the intensity if it is too much for you.

Vibration sensations

Also during one of the MRI scans (Visit 3), you will feel some non-painful vibration sensations on one finger using a vibrating device that we will comfortably attach to your finger. Before the scan begins, we will adjust the intensity of the vibration to a level that is comfortable for you. This will take place during the same scan that involves the pressure sensations described in the previous paragraph. You will not feel more than 30 of these vibrations during that time.

6. Are there any restrictions that I need to comply with if I take part?

You will be asked to refrain from consuming alcohol, smoking tobacco, or consuming any other recreational drugs for 24 hrs prior to the study visits, in case it interferes with the brain recordings.

7. What are the possible benefits of taking part?

The study does not involve any form of treatment and so you are not expected to benefit directly from participating in this study. However, information collected as part of your participation may benefit patients with chronic pain in the future.

8. What are the possible disadvantages and risks of taking part?

The study is unlikely to cause risk to your health should you take part. Some things to note are:

- Sound stimulation will be kept at a safe volume so as not to harm the ears.
- The electrical stimulator for inducing touch sensations has in-built safety cut-off limits to prevent injury and is not expected to cause harm.
- MRI scans are not known to be associated with any significant dangers, providing you do not have certain types of metal objects in your body and the proper safety procedures are followed. Most importantly, we will NOT study you if you are fitted with a heart pacemaker, mini-defibrillator or a neurostimulator; if you have surgical clips in your head; if you have suffered injuries which may have left metal particles in your eye or elsewhere in your body; or if you have an artificial heart valve. We will also ask about other kinds of surgery and metal implant which might affect your suitability. We will make sure that this is the case before we undertake the scan. The scanner you will be lying in is narrow and the noise produced by the machine is rather loud (you will be given ear plugs). If you find this or any part of the procedure too unpleasant, the scans would be stopped immediately.
- Occasionally research studies using magnetic resonance imaging reveal significant unexpected abnormalities which require medical follow-up, either for further investigation or (more rarely) treatment. The scans we do are for research purposes, but we review them carefully to avoid missing such an abnormality. We will spend a few extra minutes taking high-quality images that will be reviewed by a consultant radiologist. Such early detection has the benefit of starting treatment early but, in a small number of cases, this may have implications for future employment and insurance. As such, you should only take part in the MRI scans if you agree to the information about your scans being passed on to your General Practitioner or the appropriate specialist. Please note that the study researcher is not a radiologist, and will not be able to tell you whether or not your brain looks normal. The researcher is excluded from any potential correspondence between the radiologist, your GP and yourself. Also, please note that this is a research MRI scan, and is therefore not a substitute for a ‘medical’ MRI scan that a doctor might order to make a diagnosis. It should therefore not be seen as a ‘health check’.

- Data that is collected from EEG will not be assessed by a clinician for purposes of medical screening or diagnosis. Rather, the data will only be used for research and will not impact your clinical care.

9. What are the costs of taking part?

As this study requires you to visit the hospital and/or university at least once, and potentially on a number of occasions, you will be offered reimbursement for your time (£10 per hour), plus travel and parking expenses up to a limit of £30 per round trip. If you expect travel and parking expenses to exceed this amount, we may fund over £30 though this will have to be discussed with the research team prior to the visit.

10. What are the procedures put in place to mitigate the spread of COVID-19 at study visits?

- *Social distancing and use of personal protective equipment (PPE).* Researchers will wear face masks, gloves and potentially disposable aprons and face shields for the duration of visits.
  You are to wear a face mask for the duration of the visit (we will supply this) and adhere to physical distancing during the visit whenever possible.
- *Ventilation.* Doors and windows will be opened during EEG preparation and whereever possible during the remainder of the visit. A HEPA filter may also be used.
- *Mitigating virus spread via surfaces.* All equipment used by researchers and yourself will be cleaned before and after use with alcohol wipes. Alcohol wipes will be available for you to clean any equipment you touch, such as pens, after use. Regular hand washing will be carried out by researchers including prior to the session, after fitting the EEG cap, and at the end of the session.
- Hot and cold beverages will no longer be provided by the researchers and we recommend you bring your own drinks. You will be advised against eating during the visit, but hand washing facilities and alcohol gel will be available prior to consumption if you must eat.
- A researcher will contact you 24 hours before taking part in the study to ensure that you feel well and able to attend. The researcher will ask you if have had any symptoms of COVID-19 or if you have had recent contact with someone with COVID-19, if so, the visit will be delayed by at least 14 days (or appropriate duration of self-isolation determined by government regulations) until you are free of any symptoms.
- If the researcher develops any symptoms of COVID-19 or has recent contact with someone with COVID-19, they will self-isolate in line with government regulations and all study visits will be delayed.

- If researchers develop symptoms of COVID-19 and if you attended the lab within the last 48 hours, you will be contacted. You will be asked to contact the researcher if you develop a COVID-19 infection after the session (e.g., within 14 days).
- You will be contacted prior to visit to describe the procedures and your involvement in the study. Decisions about whether or not to attend will be fully supported and you are free to withdraw or cancel at any time.
- You will not be able to take part in the study if you do not agree to follow the measures set in place to mitigate the spread of COVID-19.

If the information in Part 1 has interested you and you are considering taking part in the study, please read the additional information in Part 2 before making any decision.

Section 2: Study Conduct

11. What if I decide I no longer wish to participate in the study?

You are free to withdraw from the study at any time without giving a reason. No questions will be asked and there will not be any ramifications. For example, your future medical treatment will not be affected in any way. You will be remunerated (pro rata) for your time spent.

Further, at any time up to one month after we have collected data from you, you may withdraw consent to use your data if you wish. All data will be deleted and not further analysed. After the one-month period, however, recordings will have been included in our analyses, and so withdrawal of your data will not be possible.

The study doctor may also choose to withdraw you from the study if they feel it is in your best interests or if you have been unable to comply with the requirements of the study.

12. What if there is a problem?

Minor complaints

If you have a minor complaint then you need to contact the researcher(s) in the first instance. Please contact Dr Christopher Brown at 0151 794 2174 or christopher.brown@liverpool.ac.uk.

Formal Complaints

If you wish to make a formal complaint or if you are not satisfied with the response you have gained from the researchers in the first instance, then please contact the Research Governance Officer on 0151 794 8290 (ethics@liv.ac.uk). When contacting the Research Governance Officer, please provide details of the name or description of the study (so that it can be identified), the researcher involved, and the details of the complaint you wish to make.

Harm

In the event that something does go wrong and you are harmed during the research you may have grounds for a legal action for compensation against the University of Liverpool but you may have to pay your legal costs.

13. Will my participation in this study be kept confidential?

All information collected about you as a result of your participation in the study will be kept strictly confidential, but if a significant abnormality is found on your scan then your GP will be informed. Your personal and medical information will be kept in a secure file and be treated in

the strictest confidence. We will not store your contact details after the study ends unless you have given us permission to do so. For example, you may wish us to keep you informed about the results of the research, or opportunities to participate in other studies that are relevant to you. You may ask to see your personal information at any time and correct any errors if necessary. If you wish to view your personal information, please write to the Liverpool University Data Protection Officer, Computing Services Department, Chadwick Building, Peach Street, Liverpool, L69 7ZF, for more information on how to do this.

Once you have agreed to participate in this study you will be allocated a unique study number which will be used on all your study documentation. Once you have completed participation in the study, your study data will only be identifiable by this unique number. Your data will therefore be fully anonymised. “Anonymised” means that your data will be labelled with a code and all personal identifying information will be removed to ensure your privacy is protected. During the study, the researchers involved with the study, and authorised staff who work for, or with, the sponsor of the study, may require access to your personal information and/or medical records to verify the data for this study and ensure that it is being conducted in accordance with UK law. All information will be treated in the strictest confidence during the review process.

14. What happens to the data?

Data protection is an important issue and we have taken a number of steps to ensure that your personal data is kept secure at all times. The University of Liverpool is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records (with your consent) in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly.

The University of Liverpool will collect information from you and/or your medical records for this research study in accordance with the Health Research Authority requirements, under the General Data Protection Regulation for health and care research.

The University of Liverpool will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study isrecorded for your care, and to oversee the quality of the study. Individuals from The University of Liverpool and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The only people in The University of

Liverpool who will have access to information that identifies you will be people who need to contact you to or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details. The University of Liverpool will keep identifiable information about you from this study for less than 3 months after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. You can find out more about how we use your information https://www.liverpool.ac.uk/legal/data_protection/. Our Data Protection Officer is Victoria Heath and you can contact them at V.Heath@liverpool.ac.uk.

Data that can be completely anonymised (for example, the EEG data), and that cannot be linked back to you personally, will be put into a publicly accessible database (e.g. the University of Liverpool institutional repository), also for at least 10 years, while copies of MRI (brain scan) data will be kept for at least 15 years by the brain imaging facility. This is part of the scientific process, allowing other scientists to replicate our results. This also greatly enhances the impact of this work on the wider research community and minimises the number of experiments that must be carried out by other researchers. Nevertheless, it means that researchers across the world may use your data for new analyses, beyond the one planned here. If you do not wish your data to be used in this way you are free to opt out of this aspect of the study. There will be no ramifications and you can still take part in all the other aspects. The only difference is that your data will only be analysed by researchers from the immediate research team.

Your information could be used for research in any aspect of health or care, and could be combined with information about you from other sources held by researchers, the NHS or government. Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. The information will only be used for the purpose of health and care research, or to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you, such as insurance. Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee.

15. What will happen to the results of the study?

The results of the study will be anonymous by the time they are in the public domain, and you will not be able to be identified from any of the data produced. When the results of this study are available they may be written into a reports for internal purposes and to inform the funder of the research, published in publically-accessible peer reviewed scientific journals and used for scientific presentations and conferences. We also plan to produce a summary of the results which will be easy for study participants to read and understand. With your consent we will send this summary to you.

16. Who is organising (sponsoring) and funding the study?

This study is sponsored by The University of Liverpool. The study is being funded by Arthritis Research UK (http://www.arthritisresearchuk.org/) to help understand and treat the causes of chronic pain.

17. Who has reviewed this study?

All research within the NHS is reviewed by an independent group of people called a Research Ethics Committee (REC), to protect your interests.

18. Further information and contact details

Please feel free to contact a member of the study team listed below for any further information on tel. 01517958054 or email pain@liverpool.ac.uk

Eleanor Brian

Dr Christopher Brown

Dr Nicholas Fallon

For written correspondence:

Christopher Brown, 1.59c Eleanor Rathbone Building, Bedford Street South, Liverpool, United Kingdom, L69 7ZA.