
Probing the Rheumatoid Arthritis Brain to Elucidate Central Pain Pathways

Pro-BEPP

Running Title	Pro-BEPP
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AMENDMENT NUMBER	DATE	PROTOCOL VERSION
1	**02.12.2021**	**2.0 –** Addition of measures of disease activity at screening
2	**18.02.2022**	**3.0 –** Addition of a second screening visit to accommodate a screening MRI scan. Addition of the option to complete select pre-treatment questionnaires remotely, reducing visit duration. Changes to follow-up time windows, from +/- 3 days to +/- 7 days. The protocol has been updated to include the above additions, and an ultra-high resolution layer specific fMRI scan in the post-treatment scanning sequence (section 6.2.1).

This study will be performed according to the UK policy framework for health and social care research (version 3.3, 07 November 2017) and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended).

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Probing the Rheumatoid Arthritis Brain to Elucidate Central Pain Pathways

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LIST OF ABBREVIATIONS

Complete as required, all abbreviations used in the protocol should be defined upon first mention and added to this table

ACR	American College of Rheumatology
AE	Adverse Event
ALFF	Amplitude of Low-Frequency Fluctuations
BOLD	Blood oxygenation level dependent
CDAI	Clinical Disease Activity Index
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Indemnity Scheme
CNS	Central Nervous System
CRP	C-reactive Protein
DMARD	Disease-Modifying Anti-Rheumatic Drug
eCRF	Electronic case report form
EL	Engagement Leads
ELISA	Enzyme-linked immunosorbent assay
EPR	Electronic Patient Record
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
MRI	Magnetic resonance imaging
GAIN	Glasgow Arthritis Involvement Network
GluCEST	Glutamate Chemical Exchange Saturation Transfer
IMID	Immune-mediated inflammatory diseases
L-IPL	Left Inferior Parietal Lobule
MRS	Magnetic Resonance Spectroscopy
MSD	Meso Scale Discovery
NRS	Numeric Rating Scale
PPI	Patient and Public Involvement
PROMIS	Patient Reported Outcome Measurement Information System
PRP	Patient Research Partner
R&D	Research and Development
RA	Rheumatoid arthritis
RACE	Research into Inflammatory Arthritis Centre Versus Arthritis

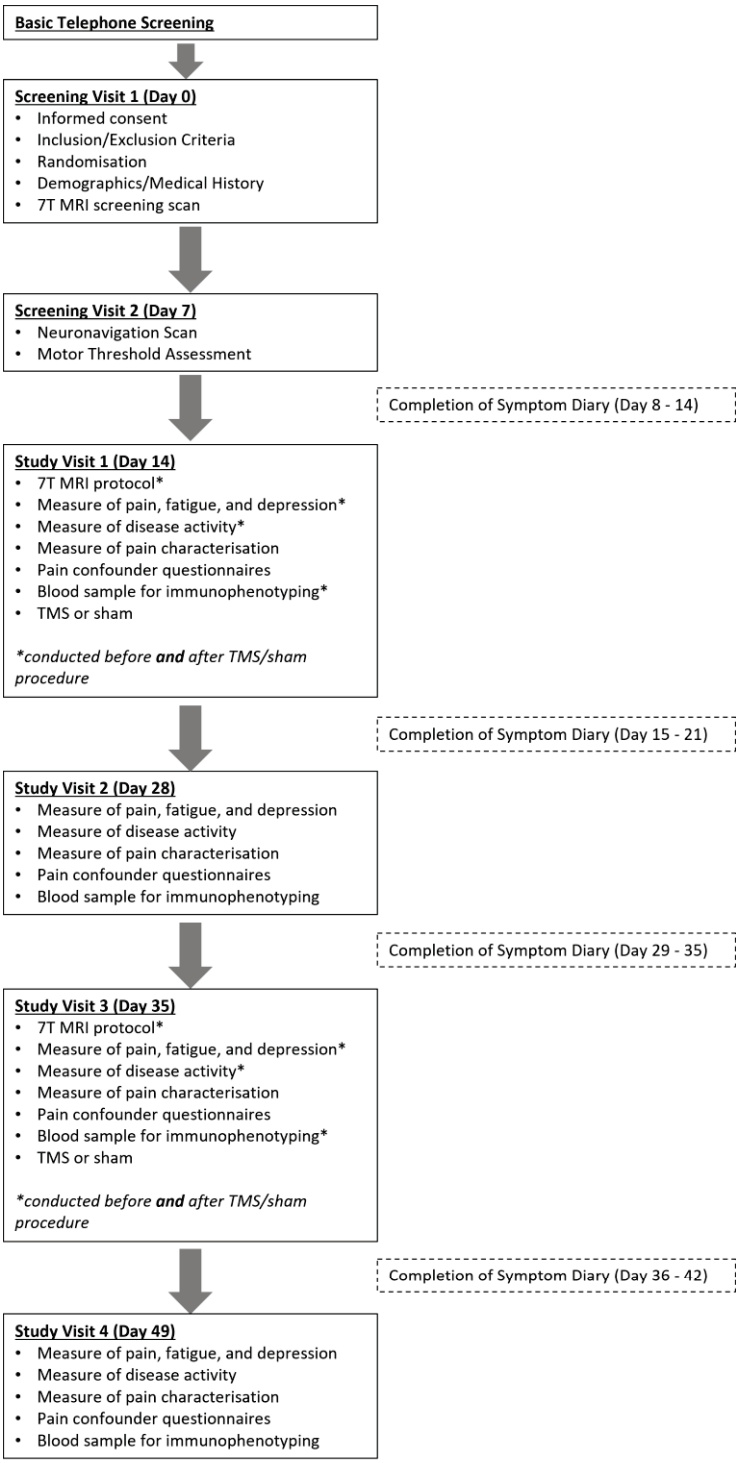
REC	Research Ethics Committee
ReHo	Regional Homogeneity
SAE	Serious Adverse Event
SADE	Serious Adverse Device Event
SDAI	Simple Disease Activity Index
7T	Tesla
TMG	Trial Management Group
TMS	Transcranial magnetic stimulation

STUDY SYNOPSIS

Title of Study	**Probing the Rheumatoid Arthritis Brain to Elucidate Central Pain Pathways**
Study Centre	University of Glasgow/NHS Greater Glasgow and Clyde
Duration of Study	24 months
Primary Objective	To evaluate changes in neural glutamate, neuronal signal cohesion and functional connectivity in RA patients following L-IPL stimulation using TMS
Secondary Objective	To evaluate changes in pain severity and characterisation, RA disease activity, sickness behaviour and peripheral inflammatory markers in RA patients following L-IPL stimulation using TMS
Primary Endpoints	The primary endpoints are - Changes in functional connectivity and neuronal signal cohesion after TMS/sham therapy, as measured by 7T MRI - Changes in glutamate signal in the L-IPL after TMS/sham therapy, as measured by 7T MRS
Rationale	Many patients with rheumatoid joint disease continue to experience significant pain despite receiving apparently optimal joint specific therapies. We believe this discrepancy relates to the existence of pain sources which are supplementary to those present in the joints. In particular, we have been among the first to report evidence implicating the brain in the generation of this disabling problem. Brain scanning methods have helped us to identify a specific region (the left inferior parietal lobule (L-IPL)) which appears to be an important link between the characteristic excessive inflammation of RA and pain processing. We hope to better examine this possible link by employing a safe, non-invasive technique called transcranial magnetic stimulation (TMS). TMS uses a magnet to influence the function of a specific region on the brain surface. We will use TMS to target the left inferior parietal lobule and then assess participants for changes in aspects of brain biology (which have been considered important in other chronic pain disorders), their pain and markers of inflammation. Due to the inherent dangers of sampling the brain, we will instead use 7T magnetic resonance imaging to make indirect measurements of brain biology, including changes in specific chemistry. This information will help us to better understand the precise role of the left inferior parietal lobule in relation to pain. The results of this modest project will inform bigger, more definitive studies and will ultimately deliver knowledge that will allow us to address the tremendous shortfall of safe and effective pain relief strategies for patients with RA and beyond.
Methodology	This randomised, sham-controlled, crossover study will allow us to test the hypothesis that systemic inflammation results in haphazard neuronal signalling and heightened centralised pain using a single session of non-invasive TMS. In order to ensure that any observed changes are specific to TMS, subjects will be randomised equally to receive an initial single session of either active or sham procedure. The latter will employ the same equipment but will not generate a magnetic effect. Subjects will be asked to return 3 weeks later to receive the alternative procedure.
Sample Size	20 participants

Screening	Patients with active RA attending clinics in NHS Greater Glasgow and Clyde will be approached to contribute to this study by the point of care team.
Inclusion Criteria	• Adults ≥ 18 years < 75 years. • Physician diagnosis of RA • ACR definition of chronic widespread pain • Able and willing to maintain medication for the 6-week study duration • CRP > 6mg/L or ESR > 20mm/hr • ≥1 swollen joint • Right-handed (to reduce neuroimaging heterogeneity).
Exclusion Criteria	• Inability to provide written informed consent. • Severe physical impairment (e.g. blindness, deafness, paraplegia). • Pregnant, planning pregnancy or breast feeding. • Severe claustrophobia precluding MRI. • Contraindications to MRI (e.g. metal implants/ pacemaker). • Contraindications to TMS (e.g. history of seizures). • Serious infection including sepsis, tuberculosis and opportunistic infections such as invasive fungal infections. • Major confounding neurological disease including Multiple Sclerosis, Stroke, Traumatic Brain Injury, Parkinson's Disease, Alzheimer's Disease
Product, Dose, Modes of Administration	A single session of transcranial magnetic stimulation (TMS) of the left inferior parietal lobule (L-IPL) will be delivered using a figure of 8 coil at 10Hz, 90% resting motor threshold intensity and 1200 pulses. The TMS pulses will be given in series of 20 trains of 6s duration (with 54s intertrain intervals).
Duration of Study Participation	6-8 weeks
Statistical Analysis	**1) Descriptive statistics and data visualization**. Median values and interquartile ranges of primary and secondary outcomes will be generated for each of the four time points. Paired plots for raw data and boxplots will be generated showing difference scores in the outcomes following sham and active TMS. **2) Hypothesis testing**. Paired-difference tests for parametric data (paired sample t-tests) will be used to test our hypotheses by comparing the change in outcomes following sham TMS to the change in outcomes following active TMS. Hypothesis testing will be two-sided with alpha = .05, and 95% confidence intervals around the contrast will be generated using bootstrapping with 20,000 resamples. **3) Effect Size:** As a simple expression of effect size, the proportion of subjects showing greater, equal and lesser reduction in glutamate between active and sham conditions will be reported. For the calculation of sample size estimates for future studies, the standardized mean difference effect size for within-subject designs (d-z) will be calculated. **4) Outcome inter-relationships**: Exploratory correlations will examine the relationships between the different outcomes and their change

1 STUDY FLOW CHART



2 SCHEDULE OF ASSESSMENTS

Study Procedure	**Screening Visit 1**	**Screening visit 2†**	**Visit 1 (+/- 7 days)**	**Visit 2 (+/- 7 days)**	**Visit 3 (+/- 7 days)**	**Visit 4 (+/- 7 days)**
Informed consent	✓					
Inclusion/exclusion criteria	✓					
Neuronavigation Scan		✓				
Motor Threshold Assessment		✓				
7T structural scans	✓					
Randomisation	✓					
Demographics	✓					
BMI	✓					
Family Medical History	✓					
Completion of Symptom Diary††§		✓	✓	✓	✓	
7T magnetic resonance protocol			✓*		✓*	
Pain, fatigue, and depression severity			✓*	✓	✓*	✓
Measure of disease activity	✓		✓	✓	✓	✓
Sickness Questionnaire			✓*	✓	✓*	✓
Pain confounder questionnaires§			✓	✓	✓	✓
Michigan Body Map Regional Pain§			✓	✓	✓	✓
Blood sample for immunophenotyping†††			✓*	✓	✓*	✓
TMS or sham procedure			✓		✓	
Recording of Adverse Events			✓	✓	✓	✓

† Screening visit will be conducted at the Centre for Cognitive Neuroimaging, University of Glasgow
†† Symptom diary will be completed for the 7 days following each visit
††† Blood sample schedule outlined in 6.4 LABORATORY TESTS
* Procedure will be performed twice; before ***and*** after TMS/Sham therapy
§ Option to complete questionnaires remotely to reduce visit length

3 INTRODUCTION

3.1 BACKGROUND

Rheumatoid arthritis (RA) is a common disease which is characterised by severe joint inflammation and chronic pain[1]. The discovery of new joint specific treatments has transformed patient outcomes and yet most patients, even those whose joints respond fully to these treatments, continue to experience significant levels of pain[2, 3]. We therefore believe that RA pain is caused by alternative sources in addition to the joints.

Our group are pioneering the investigation of a possible link between the brain and the pain which RA patients experience. By employing sophisticated brain scanning methods, we have shown that high levels of pain and blood inflammation are associated with changes within a specific region of the brain known as the left inferior parietal lobule (L-IPL)[4]. This region exhibited abnormal connections with other brain regions already known to be associated with pain in another chronic pain disorder called fibromyalgia. Fibromyalgia is a musculoskeletal condition which is not classically related to high levels of blood inflammation, although, interestingly, it is not uncommon for it to co-exist in RA patients[5, 6]. In light of our preliminary brain scan studies, we now think that fibromyalgia in the context of RA may be partially influenced by inflammation.

In order to fully understand the precise processes that lead to this potential relationship, it is important to characterise the biological abnormalities that underlie our brain scan observations. Previous animal experiments have consistently observed abnormalities, such as high levels of the brain chemical glutamate and haphazard brain activity, in the context of inflammation. Conducting similar experiments in humans is not practical due to the inherent dangers of sampling live brain tissue. Instead, neuroscientists commonly use non-invasive methods to manipulate specific parts of the brain in order to better understand how they function. In conjunction, the latest scanners are now able to indirectly measure the effect of the brain modulation on relevant aspects of brain biology without the need to remove tissue[7]. This information will help us to better understand the relationship between inflammation and pain in the RA brain.

3.2 RATIONALE

Rheumatoid Arthritis-related pain is only partially explained by joint specific inflammation. Despite excellent control of peripheral inflammation by contemporary immune modulatory regimes, as many as 50% of patients continue to report disabling levels of pain, thus comprising an urgent unmet clinical need[2, 3].

We have been among the first to evidence a contributory role of the central nervous system (CNS) as an explanation for this apparent disconnect[4, 8]. Our cross-sectional neuroimaging studies have implicated the left inferior parietal lobule of the brain as a critical interface between inflammation and pain. Not only did this region associate with levels of patient reported pain and indicators of systemic inflammation, but it was found to be functionally hyperconnected to brain networks established to be pro-nociceptive in CNS based chronic pain disorders such as fibromyalgia. In parallel, preclinical experiments suggest that systemic inflammation leads to heightened glutamate neurotransmission, which in turn results in disorganised neuronal signal activity and ultimately altered functional connectivity between regions of the brain. In RA patients, we hypothesise that systemic inflammation-related neural glutamate enhancement triggers chaotic neuronal signalling, followed by compensatory hyperconnectivity with pro-nociceptive functional brain networks. Thereby, we believe that dysfunctional inflammatory processes in RA not only mediate nociception in vulnerable joints but also nociception in vulnerable regions of the brain.

Given the clear practical constraints of sampling fresh human brain tissue, we propose to test our hypothesis by combining state-of-the-art non-invasive brain modulatory techniques alongside leading-edge neurobiological surrogate imaging measures. Transcranial magnetic stimulation (TMS) is the neural modulatory probe of choice for neuroscientists seeking to infer causality of specific brain cortical regions[9, 10]. Ultra-high resolution 7T MRI enables measurement of functional connectivity and haphazard neuronal signal activity at significantly superior spatial resolution compared to standard 3T approaches and can uniquely assess regional glutamate.

As a critical first step, this feasibility study aims to pilot a transcranial magnetic stimulation (TMS) protocol designed to target the L-IPL in RA. We will evaluate its effect employing ultra-high resolution 7T functional and glutamate measures. This novel project will inform a larger study which will aim to provide more robust evidence for the proposed neural pain interface between systemic inflammation and pain. Such knowledge could potentially support the analgesic testing of existing compounds e.g. alternative/augmented immunosuppressants or neural glutamate modulatory agents; and reverse translated in order to more precisely dissect the culprit mechanisms which in turn may inform the development of novel pain therapeutics. Both represent core aims of Versus Arthritis and address critical priorities among the patient populations that we serve.

3.3 STUDY HYPOTHESIS

We believe that the left inferior parietal lobule of the brain is a key region where inflammation and pain communicate in RA. Specifically, we hypothesise that inflammation leads to high levels of glutamate in the left inferior parietal lobule and subsequent haphazard functioning of this area. This then leads to abnormal communication with other regions of the brain such as those known to be important to pain processing in fibromyalgia. Ultimately, we expect these processes to alter patients' overall experience of pain.
If correct, we would expect a normalisation of left inferior parietal lobule activity to reduce glutamate levels and rebalance the functioning of the proposed pain systems in 'inflamed' RA patients.

4 STUDY OBJECTIVES

1) Determine the effects of L-IPL TMS on functional connectivity and neuronal signal cohesion.
2) Determine the effects of TMS on MRS Glutamate signal in the L-IPL.
3) Determine the effects of TMS on pain severity and disease activity in RA patients.

4.1 PRIMARY ENDPOINT

- Changes in functional connectivity and neuronal signal cohesion after TMS/sham therapy, as measured by 7T MRI
- Changes in glutamate signal in the L-IPL after TMS/sham therapy, as measured by 7T MRS

4.2 SECONDARY ENDPOINT(S)

Changes in components of sickness behaviour, pain severity, disease activity and inflammation after TMS/sham therapy as follows:

- Pain severity as measured by the Michigan Body Map Regional Pain and NRS-Pain
- RA disease activity as measured by SDAI, CDAI
- Sickness behaviour as measured by the Sickness Questionnaire

- Putative pain confounders as measured by PROMIS-Fatigue, PROMIS-Depression, PROMIS-Anxiety, PROMIS-Sleep Related Impairment, PROMIS-Physical functioning short form, PROMIS-Pain interference and ACR Fibromyalgia Scale
- Blood protein levels of inflammatory cytokines/chemokines

5 STUDY DESIGN

The study design is detailed below and is summarised in the STUDY FLOW CHART and **Error! Reference source not found.**. The trial is a single-centre, randomised sham-controlled crossover study to test the hypothesis that normalisation of left inferior parietal lobule activity using TMS will reduce glutamate levels and rebalance the functioning of the proposed pain systems in 'inflamed' RA patients.

All of the study research data/ indices including the outcomes of study measures and samples will be shared with our collaborators in the University of Michigan. No personal data will be exported to our co-investigators at University of Michigan, but non-personal information may be transferred. The data transferred to the University of Michigan will include the study code/age/gender and questionnaire data. The University of Michigan will not have access to the pseudoanonymised key which will be kept within NHS GG&C only, therefore data will be anonymised to the University of Michigan investigators and pseudoanonymised to NHS GG&C/University of Glasgow investigators. The University of Michigan will undertake collaborative analyses; an appropriate Data Transfer Form and Controller to Controller Agreement will be completed.

5.1 STUDY POPULATION

The study will involve participants aged over 18 years with active inflammatory RA who meet the inclusion criteria below and who have none of the specified exclusion criteria. All will give full informed consent.
Rheumatoid arthritis patients attending secondary care clinics in NHS GG&C and in NHS Lanarkshire will be screened for eligibiity. NHS Lanarkshire will act as a participant identification centre (PIC) and all study participants will undertake study procedures at the University of Glasgow and the Queen Elizabeth University Hospital(NHS GG&C).

5.2 INCLUSION CRITERIA

- Adults ≥ 18 years < 75 years.
- Physician diagnosis of RA
- ACR definition of chronic widespread pain
- Able and willing to maintain usual/ medication for the 6-week study duration
- CRP > 6mg/L or ESR > 20mm/hr
- ≥1 swollen joint
- Right-handed (to reduce neuroimaging heterogeneity)

5.3 EXCLUSION CRITERIA

- Inability to provide written informed consent.
- Severe physical impairment (e.g. blindness, deafness, paraplegia).
- Pregnant, planning pregnancy or breast feeding.
- Severe claustrophobia precluding MRI.
- Contraindications to MRI (e.g. metal implants/ pacemaker).
- Contraindication to TMS (e.g. history of seizures).

- Serious infection including sepsis, tuberculosis and opportunistic infections such as invasive fungal infections.
- Major confounding neurological disease including Multiple Sclerosis, Stroke, Traumatic Brain Injury, Parkinson's Disease, Alzheimer's Disease

5.4 CONCOMITANT MEDICATION

All Rheumatoid Arthritis therapies (including DMARDs/steroids/biologics) are permitted but must stay constant for the duration of the study. In exceptional circumstances, intra-articular/ intra-muscular steroids will be permitted according to investigator discretion.

5.5 IDENTIFICATION OF PARTICIPANTS AND CONSENT

Patients with active RA attending rheumatology outpatient clinics in NHS Greater Glasgow and Clyde and in NHS Lanarkshire will be notified of the study by the direct care team and will be provided with a patient information sheet. The patient will be asked to consent to a member of the research team contacting them by phone at least 24 hours later to gauge their interest in the study and allow them to ask any questions. This verbal agreement to be contacted by researchers will be documented by the direct care team in clinical record. Eligibility will be confirmed by a medically qualified doctor who is part of both the clinical/research team.
Contact details of interested patients will be shared by the clinical team with the research team via NHS to NHS email.

If the patient assents, they will be contacted by phone by a member of the research team to go through basic screening, address any queries, verify right hand dominance and check for MRI and significant medical condition contraindications. At this stage, potential participants will be invited to attend screening and consent visits that will be conducted at the Imaging Centre of Excellence (ICE) at the Queen Elizabeth University Hospital and the Centre for Cognitive Neuroimaging at the University of Glasgow. At these meetings, subjects will be asked again if they have any questions. Participants will undergo informed consent where two copies of the consent form will be signed (one each for the participant and the site file). A copy of the signed consent form will be inserted into the patient's record or scanned into the electronic patient record (EPR). A letter will be sent to the patient's GP informing them of their participation in the study.

Eligibility will be confirmed by a medically qualified investigator and consent will be taken by a member of the research team.

The research team comprises individuals who help to coordinate and perform the study in addition to individuals from the direct clinical care team. In addition to the clinical team, the research team requires access to the patient's medical record to be able to comprehensively collect necessary clinical characterization e.g blood results and validate patient reports.

5.6 RANDOMISATION & BLINDING

This is a randomised, sham-controlled, crossover study. Once participants have given consent and been fully screened for study eligibility, they will be randomised to receive either a single session of active TMS procedure to the L-IPL or a TMS sham procedure which will not modulate the brain. Provided the first session causes no reason to withdraw the participant, they will return 3 weeks later to receive the alternative TMS procedure to that they had undergone originally.

In order to optimise participant blinding, we will employ a sham coil which mimics the clicking and scalp sensations.

5.7 WITHDRAWAL OF PARTICIPANTS

The patient can decide to withdraw from the clinical trial at any time for no reason. The Chief Investigator (CI) or co-investigators also have the right to withdraw patients from the study if deemed in the best interests of the patient or in the event of Adverse Events (AEs), protocol violations, administrative or other reasons. Full details of withdrawal should be recorded on the electronic Case Report Form (eCRF).

Participants may decide to withdraw their initial consent for this study, at this point no further information regarding the participant will be collected. Data relating to the patient that has been collected up to the point of withdrawal will still be used. Any stored blood samples that can still be identified as the participants will be destroyed.

6 TRIAL PROCEDURES

6.1 STUDY SCHEDULE

The study will comprise of a total of 6 research visits.

6.1.1 Screening visit 1 (Day 0)

This screening visit will be conducted at the Queen Elizabeth University Hospital.

- Informed consent
- Review of inclusion / exclusion criteria
- Disease activity (SDAI / CDAI)
- 7T structural scans
- Randomisation
- Demographics
- BMI
- Medical History

Estimated visit time 1 hour

6.1.2 Screening visit 2 (Day 7) (+/- 7 days)

This screening visit will be conducted at the Centre for Cognitive Neuroimaging, University of Glasgow.

- Neuronavigation scan
- Motor threshold assessment
- Completion of symptom diary (to be done at home, Days 8-14)

Estimated visit time 1 hour

6.1.3 Visit 1 (Day 14) (+/- 7 days)

Visit 1 will be conducted at the Queen Elizabeth University Hospital

- 7T Neuroimaging protocol*
- Michigan Body Map Regional Pain§
- NRS for pain, fatigue, and depression*
- McGill Pain Questionnaire§
- Disease activity (SDAI / CDAI)
- Sickness Questionnaire*
- Pain confounder questionnaires§:
    - PROMIS-Fatigue (16-items)§
    - PROMIS-Depression (8 items)§
    - PROMIS-Anxiety (8 items)§
    - PROMIS-Sleep Related Impairment (8 items)§
    - PROMIS-Physical Functioning Short Form (8-items)§
    - PROMIS-Pain Interference (8-item)§

  - ACR Fibromyalgia Scale§
- Venous blood sample for peripheral immunophenotyping*
- TMS or sham procedure
- Completion of symptom diary (to be done at home, Days 15-21)

**will be conducted before and after TMS/sham procedure*
§has the option to be completed remotely to reduce visit time

Estimated visit time 4 hours

6.1.4 Visit 2 (Day 28) (+/- 7 days)

Visit 2 will be conducted at the Queen Elizabeth University Hospital

- Michigan Body Map Regional Pain§
- NRS for pain, fatigue, and depression
- McGill Pain Questionnaire§
- Disease activity (SDAI / CDAI)
- Sickness Questionnaire
- Pain confounder questionnaires§:
  - PROMIS-Fatigue (16-items)§
  - PROMIS-Depression (8 items)§
  - PROMIS-Anxiety (8 items)§
  - PROMIS-Sleep Related Impairment (8 items)§
  - PROMIS-Physical Functioning Short Form (8-items)§
  - PROMIS-Pain Interference (8-item)§
  - ACR Fibromyalgia Scale§
- Venous blood sample for peripheral immunophenotyping
- Completion of symptom diary (to be done at home, Days 29-35)

§has the option to be completed remotely to reduce visit time

Estimated visit time 1.5 hours

6.1.5 Visit 3 (Day 35) (+/- 7 days)

Visit 3 will be conducted at the Queen Elizabeth University Hospital

- 7T Neuroimaging protocol*
- Michigan Body Map Regional Pain§
- NRS for pain, fatigue, and depression*
- McGill Pain Questionnaire§
- Disease activity (SDAI / CDAI)
- Sickness Questionnaire*
- Pain confounder questionnaires§:
  - PROMIS-Fatigue (16-items)§
  - PROMIS-Depression (8 items)§
  - PROMIS-Anxiety (8 items)§
  - PROMIS-Sleep Related Impairment (8 items)§
  - PROMIS-Physical Functioning Short Form (8-items)§
  - PROMIS-Pain Interference (8-item)§
  - ACR Fibromyalgia Scale§
- Venous blood sample for peripheral immunophenotyping*
- TMS or sham procedure

- Completion of symptom diary (to be done at home, Days 36-42)

**will be conducted before and after TMS/sham procedure*
§has the option to be completed remotely to reduce visit time

Estimated visit time 4 hours

6.1.6 Visit 4 (Day 49) (+/- 7 days)

Visit 4 will be conducted at the Queen Elizabeth University Hospital

- Michigan Body Map Regional Pain§
- NRS for pain, fatigue, and depression
- McGill Pain Questionnaire§
- Disease activity (SDAI / CDAI)
- Sickness Questionnaire
- Pain confounder questionnaires§:
    - PROMIS-Fatigue (16-items)§
    - PROMIS-Depression (8 items)§
    - PROMIS-Anxiety (8 items)§
    - PROMIS-Sleep Related Impairment (8 items)§
    - PROMIS-Physical Functioning Short Form (8-items)§
    - PROMIS-Pain Interference (8-item)§
    - ACR Fibromyalgia Scale§
- Venous blood sample for peripheral immunophenotyping

§has the option to be completed remotely to reduce visit time

Estimated visit time 1.5 hours

6.2 BRAIN IMAGING PROTOCOLS

6.2.1 MRI and MRS Protocols

The 7T multimodal MRI brain scanner is housed within the Imaging Centre of Excellence at the QEUH, Glasgow. An ultra-high resolution 7T multimodal MRI brain scan using a MAGNETOM Terra 7T scanner (Siemens Healthcare, Erlangen, Germany) and a single channel transmit, 32 channel receive radiofrequency head coil (Nova Medical, Wilmington, MA) will obtain neurobiological surrogate measures of structure, functional connectivity, neural signal cohesion and glutamate:

Screening (screening visit 1):

a) **Structural MRI scan -** A whole-brain T1-weighted images will be collected using a twice magnetization-prepared rapid gradient echo (MP2RAGE) sequence, with a scanning time of 10 minutes. The scan will be processed to parcellate the brain and mark the region of interest (left IPL).
b) **Spectroscopy voxel scan -** A magnetic resonance scan will be undertaken to identify the voxel of interest for spectroscopic imaging. A single voxel sequence will be employed with semi-LASER preparation. An approximately 20x20x20 mm3 voxel will be placed in the L-IPL, taking approximately 5 minutes.

Neuroimaging Protocol (visit 1 and visit 3):

a) **Functional connectivity and neuronal signal cohesion data** – a resting state BOLD-fMRI scan will be undertaken. Functional connectivity MRI (fcMRI) investigations are conducted with subjects resting in the scanner. Approximately ten minutes of whole-brain resting state fMRI data

will be collected using a simultaneous-multi-slice (SMS) echoplanar- imaging (EPI) sequence of factor=4, with echo time (TE) = 25ms, repetition time (TR) = 1500ms, flip angle (FA) = 65°, field of view=192 × 192mm2 with 96 slices of 1.5mm isotropic resolution. A whole-brain T_1- weighted structural image will also be collected using a twice magnetization-prepared rapid gradient echo (MP2RAGE) sequence. During the resting state, subjects will be instructed not to undertake any particular task and to stay awake with their eyes open on a fixation cross. Whole brain coverage will be performed. Data will be pre-processed and analysed using software such as statistical parametric mapping (SPM) software package version 12 (SPM12, Wellcome Department of Cognitive Neurology, London, United Kingdom) and the Conn (Cognitive and affective neuroscience laboratory, MIT, Cambridge, USA) functional connectivity toolbox, all running on MATLAB. Upon collection of resting state fcMRI data, the pre-processing steps necessary for each analysis will be included such as the removal of physiological artefacts, motion correction, realignment, registration, normalization and smoothing. Connectivity indices will be generated from matrices informed by our a priori determined regions of interest and standard grey matter atlases. Moreover, layer-dependant connectivity and network comparison will be performed.

Regarding BOLD oscillatory markers of neural signalling cohesion: Regional homogeneity (ReHo) and Amplitude of Low-Frequency Fluctuations (ALFF) are two complementary methods used to study the regional neural activity. They can be estimated using MATLAB based software such as REST (http://restfmri.net/forum/index.php?q=rest). The ReHo analysis is a voxel-based measure of the similarity using Kendall's coefficient concordance between the BOLD time-series of a given voxel and its nearest neighbours. The ReHo measures the synchrony of adjunct regions and can be used to evaluate the consistency of local functional activities in a brain area. While the ALFF approach measures the total power of the BOLD signal within the low-frequency range between 0.01 and 0.1 Hz. ALFF has been proven to be a valuable parameter to reflect the power of regional spontaneous neuronal activity.

b) **Glutamate Imaging** – a magnetic resonance spectroscopy scan will be undertaken in order to detect the glutamate concentration. A single voxel sequence will be employed with semi-LASER preparation. An approximately 20x20x20 mm3 voxel will be placed in the L-IPL and shimming of the static magnetic field will be performed using advanced methods best suited to MRS acquisition at 7T, such as FASTESTMAP. Spectra will be preprocessed in the MATLAB based tool MRspa, then analysed and quantified using LCModel.

In addition, experimental multi-voxel techniques will be explored to investigate the utility of quantitative maps of glutamate concentration across the brain. This will be in the form of the Accelerated magnetic resonance SPectroscopic Imaging using REadout Segmentation (ASPIRES) technique. This is a multi-voxel spectroscopic technique which has been developed in-house, building on previous work, and is based on the well-known Echo-Planar Spectroscopic Imaging (EPSI) method. ASPIRES uses readout segmentation to nullify the spectral bandwidth limitations of standard EPSI methods at 7T and undersampling schemes with advance compressed sensing reconstruction to allow for significantly shorter, clinically viable acquisition times.

c) **Layer Specific fMRI scan -** a laminar based resting-state fMRI will be collected using A C2P sequence with multiband from CMRR (University of Minnesota) with spin-echo excitation sequence. Sub-millimetre fMRI data will be analysed using BrainVoyager software. Pre-processing and analysis pipeline will include segmentation of the cortical layers, motion correction, filtering and up-sampling functional data, co-registration with anatomical data, estimation the interaction across cortical layers within the IPL and between IPL layers and other ROIs.

6.3 STUDY OUTCOME MEASURES

6.3.1 Primary Outcome Measure(s)

The primary outcome measures will be:

1. Changes in functional connectivity and neuronal signal cohesion as measured by 7T MRI
2. Changes in glutamate signal in the L-IPL as measured by 7T MRS

before and after TMS/sham procedure.

6.3.2 Secondary Outcome Measure(s)

The secondary outcome measures will be:

1. Changes in pain severity as measured by the Pain NRS
2. Changes from the Michigan Body Map Regional Pain
3. Changes in RA disease activity as measured by SDAI, CDAI
4. Changes in putative pain confounders as measured by PROMIS-Fatigue, PROMIS-Depression, PROMIS-Anxiety, PROMIS-Sleep Related Impairment, PROMIS-Physical functioning short form, PROMIS-Pain Interference and ACR Fibromyalgia Scale
5. Changes in blood protein levels of inflammatory cytokines/chemokines

before and after TMS/sham procedure (1) and (5).
before TMS/sham procedure (2), (3) and (4).

6.4 LABORATORY TESTS

Sample Type	Screening visit 1	Screening visit 2	Visit 1†		Visit 2	Visit 3†		Visit 4
SST tube (8.5ml)			✓	✓	✓	✓	✓	✓
EDTA tube (4ml)			✓	✓	✓	✓	✓	✓
EDTA tube (10ml x 2)			✓	✓		✓	✓	
PAXgene RNA Tube (2.5ml)*			✓	✓		✓	✓	

† Blood samples will be collected before and after TMS/sham procedure at these visits.
* This blood sampling will be optional at the discretion of the CI.

Blood samples will be processed and analysed as described in the Pro-BEPP Lab Protocol. Blood samples will be obtained and RNA measured for cytokines, chemokines and other proteins in order to help us measure different disturbances of the immune system in relation to rheumatoid arthritis and how they relate to the brain's pain centres.

At the end of the study, samples will be transferred to the auspices of the accredited NHS Greater Glasgow and Clyde Biorepository and stored for up to 10 years and disposed of after storage in accordance with the Human Tissue Authority's Code of Practice.

7 Study Device

Participants who are eligible for the study will receive **transcranial magnetic stimulation** using a 70 mm Double Coil connected to Super-Rapid magnetic stimulator, Magstim Co., UK. The coil and stimulator are developed and manufactured in accordance with ISO 13485:2003 and are CE marked under the Medical Device Directive (93/42/EEC).

Figure 1. Magstim Super-Rapid magnetic stimulator and 70 mm Double Coil

Further detail of the device and schedule is given below.

7.1 TRANSCRANIAL MAGENTIC STIMULATION

7.1.1 Neuronavigation Scan

As part of screening visit 2, and in preparation of the transcranial magnetic stimulation/scanning session, we will identify the optimal spot on the participants head to position the stimulation coil. For precise TMS coil positioning, TMS neuronavigation will be used (Brainsight®). This is to optimize stimulation accuracy in order to reach the area of the brain where stimulation is likely to have the best effect. To do so, the participant will be asked to wear a headband and head cap while sitting on a chair in a room.We will use an individual structural brain scan (the 7T scan performed at screening visit 1) and an optical system (camera, sensors and a digital pen) that will allow us to identify the spot on their head that is above the area in the brain that we will stimulate. We will then write on the head cap the stimulation spot, to be used in the next session. The procedure is non-invasive, painless and safe and there are no known or foreseeable risks or side effects. The TMS target site will be identified using MNI coordinates (group averaged) from our original fMRI connectivity work on RA patients.

7.1.2 Motor Threshold Assessment

Screening visit 2 will also include assessment of the resting motor threshold. This will be used to standardise the intensity of active TMS used in a subsequent session. As is normal practice, single pulse TMS will be used to stimulate the left motor cortex, which will be located with the aid of neuronavigation. The motor threshold is the minimum intensity required to elicit a motor evoked potential in the contralateral hand in at least 50% of trials. This threshold is affected by individual differences in anatomy and cortical excitability, and therefore varies between participants.

7.1.3 TMS Schedule & Administration

Active TMS will consist of a single session of 20 minutes. A figure of 8 coil will be used at 10Hz, 90% resting motor threshold intensity and 1200 pulses. The TMS pulses will be given in series of 20 trains of 6s duration (with 54s intertrain intervals).

7.1.4 Rationale for Chosen Dose

The high-frequency repetitive TMS (rTMS) protocol has been extensively used to interfere with parietal lobe network activity. In healthy participants, high frequency (10Hz) rTMS interacts with large-scale oscillatory network activity of the parietal lobe in the alpha band, causing changes in perceptual thresholds across multiple sensory modalities. Likewise, in healthy participants, high-frequency rTMS over the L-IPL reconfigures cortico-cortical network properties as revealed by fMRI. And in chronic pain patients, high frequency rTMS appears to relieve pain. Furthermore, there is evidence of analgesic efficacy in patients with fibromyalgia where high frequency rTMS has been applied to nonmotor areas.

7.1.5 Sham Procedure

Sham TMS will be applied for the exact same duration with the identical pulse sequence but using a sham TMS coil (Magstim Co., UK). This is a replica of the active figure of 8 coil and produces similar peripheral effects to the active coil (such as TMS coil clicks) but does not produce electromagnetic fields penetrating the skull.

8 RISK ASSESSMENT AND ADVERSE EVENTS

8.1 RISK ASSESSMENT

Transcranial magnetic stimulation has been used in a growing number of laboratories worldwide since 1984, however there are some potential adverse effects from TMS. Contraindications will be excluded through careful screening. All precautionary measures will be taken to avoid adverse events and safety guidelines will be rigorously followed. TMS is considered safe for studies in both healthy participants and patients when applied within the safety guidelines and is regarded as having a less than minimal risk to study participants. All contraindications and potential adverse effects will be disclosed to the participants in the Participant Information Sheet.

Common adverse effects:

Headaches and/or Neck Pain: Up to 10% of subjects undergoing TMS experience headaches or neck pain, which are believed to be due to muscle tension. All prior cases of headaches induced by TMS have promptly resolved with a single dose of paracetamol or aspirin. In some cases, TMS may cause facial discomfort on the same side of stimulation.

Hearing Problems: TMS produces a loud clicking sound when the current is passed through the stimulation coil. The peak sound pressure associated with the TMS pulse has been measured in a safety study. At a distance of 10cm and with maximum TMS intensity (100% stimulator output), the TMS pulse creates very brief (< 300 micro-sec) peak sound pressure levels of 110 dB (duration of bi-phasic TMS pulse: 300 micro-sec). Given that the threshold limits of impact noise would be reached only after 1’000-10’000 pulses per day (based on American Conference of Governmental Industrial Hygienists), the risk of TMS noise is considered small even without hearing protection.

Rare adverse effects:

Syncope: Fainting can occur due to anxiety and psycho-physical discomfort during testing and treatment with TMS. Subjects will be monitored for feeling any signs or symptoms of a pending syncopal event (i.e. feeling “dizzy, lightheaded or going to pass out”). If this is the case, TMS will immediately be stopped and the participant will be assisted.

Seizures: TMS can cause a seizure; however, this is an extremely rare problem. Fewer than 25 cases have been reported from the thousands of studies conducted internationally and the risk of a seizure from repeated courses of TMS is substantially less than one in a thousand. To make the participants’ risk as small as possible, the investigators will follow all precautions that are recommended by the International Society for Transcranial Stimulation and mentioned in the 2008 updated safety guidelines of The Safety of TMS Consensus Group.

Memory: TMS could induce transient and weak changes in memory, attention and other cognitive and mental functions up to maximally an hour after TMS. This is a rare risk.

8.2 ADVERSE EVENTS (AEs)

An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

Note 1 to entry: This definition includes events related to the investigational medical device or the comparator.

Note 2 to entry: This definition includes events related to the procedures involved.
Note 3 to entry: For users or other persons, this definition is restricted to events related to the use of investigational medical devices.

8.3 SERIOUS ADVERSE EVENT (SAE)

An adverse event that led to any of the following:

a) death,
b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:
    1) a life-threatening illness or injury, or
    2) a permanent impairment of a body structure or a body function including chronic diseases, or
    3) in-patient or prolonged hospitalisation, or
    4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c) foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment

Note 1 to entry: Planned hospitalisation for a pre-existing condition, or a procedure required by the CI without serious deterioration in health, is not considered a serious adverse event.

8.4 SERIOUS ADVERSE DEVICE EVENT (SADE)

A serious adverse device effect (SADE) is any adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. A SADE may be anticipated or unanticipated.

Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Unanticipated serious adverse device effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

8.5 RECORDING AND REPORTING OF ADVERSE EVENTS

Reports of non-serious Adverse Events (AE), Serious Adverse Events (SAE), serious adverse device events (SADE) or other errors outside of what is foreseen in the protocol (irrespective if a clinical event has occurred) will be reported to the CI and will be submitted to the Research Ethics Committee (REC) using the Non-CTIMP safety report to REC form.

Only reports of SAEs, non-serious AEs or SADEs that are 1. related to the study (i.e. they resulted from administration of any of the research procedures) and 2. unexpected (USADE) should be submitted.

These should be sent within 15 days of the CI becoming aware of the event. There is no requirement for annual safety reports in addition to the information provided through the annual progress report.

9 STATISTICS AND DATA ANALYSIS

9.1 STATISTICAL ANALYSIS PLAN

The study will have a comprehensive Statistical Analysis Plan, which will govern all statistical aspects of the study, and will be agreed by the Trial Management Group (TMG) before any unblinded data is seen.

The primary outcomes measures are changes in functional connectivity and neuronal signal cohesion as measured by 7T MRI and changes in glutamate signal in the L-IPL as measured by 7T MRS, before and after TMS/sham procedure in patients with RA.

The secondary outcome measures are changes in pain severity, changes in RA disease activity, changes in putative pain confounders and changes in inflammatory cytokines/chemokines before and after TMS/sham procedure in patients with RA.

1) Descriptive statistics and data visualization. Median values and interquartile ranges of primary and secondary outcomes will be generated for each of the four time points. Paired plots for raw data and boxplots will be generated showing difference scores in the outcomes following sham and active TMS.

2) Hypothesis testing. Paired-difference tests for parametric data (paired sample t-tests) will be used to test our hypotheses by comparing the change in outcomes following sham TMS to the change in outcomes following active TMS. Hypothesis testing will be two-sided with alpha = .05, and 95% confidence intervals around the contrast will be generated using bootstrapping with 20,000 resamples.

3) Effect Size: As a simple expression of effect size, the proportion of subjects showing greater, equal and lesser reduction in glutamate between active and sham conditions will be reported. For the calculation of sample size estimates for future studies, the standardized mean difference effect size for within-subject designs (d-z) will be calculated (Reference 40).

4) Outcome inter-relationships: Exploratory correlations will examine the relationships between the different outcomes and their change

9.2 SAFETY ANALYSIS

The safety data (serious adverse events) – both numbers of subjects and events – will be summarised overall using descriptive statistics.

9.3 SOFTWARE FOR STATISTICAL ANALYSIS

The statistical software to be used will be specified in the Statistical Analysis Plan. It is likely to be either SAS 9.4 for Windows, Cary, NC, USA or R version 4.0 (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.) or higher versions of those programs.

9.4 SAMPLE SIZE

Although inadequately powered to investigate the specific relationship between pain and the MRI metrics, changes in glutamate concentration and functional connectivity pre- and post-TMS have

previously been measured at 3T in sample sizes of n<20. Likewise, changes in pain experience after rTMS have been reported in studies with sample sizes of n<20.

9.5 MANAGEMENT AND DELIVERY

All files will receive a Digital Object Identifier (DOI), with associated metadata being listed in the University of Glasgow Research Data Registry and the DataCite metadata store. The DOI of each dataset will be included in any publication reporting it, allowing each dataset to be identified and accessed by researchers reading the publication. DOIs will also be linked with appropriate records in the University's publication repository to enhance visibility of datasets

10 TRIAL CLOSURE / DEFINITION OF END OF TRIAL

The trial will end once last participant has completed the last visit.

11 DATA HANDLING

11.1 CASE REPORT FORMS / ELECTRONIC DATA RECORD

An eCRF will be used to collect study data. The eCRF will be developed by the study team using Castor and access to the eCRF will be restricted, with only authorised, site-specific personnel able to make entries or amendments to their participants' data. It is the investigator's responsibility to ensure completion and to review and approve data captured in the eCRF.

Data will be validated at the point of entry into the eCRF and at regular intervals during the study. Data discrepancies will be flagged to relevant members of the research team and any data changes will be recorded in order to maintain a complete audit trail (e.g. reason for change, date change made, who made change).

11.2 RECORD RETENTION

To enable evaluations and/or audit from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link record), all original signed informed consent forms, serious adverse event forms, source documents, and detailed records of treatment disposition in accordance with ICH GCP, local regulations, whichever is longer. The University of Glasgow as per its Code of Good Research Practice will keep pseudonymised research data for 10 years after the study ends.

12 TRIAL MANAGEMENT

12.1 ROUTINE MANAGEMENT OF TRIAL: TRIAL MANAGEMENT GROUP

The trial will be co-ordinated by the Trial Management Group (TMG). The TMG normally includes those individuals responsible for the day-to-day management of the trial, such as the CI, statistician, project manager, research nurse, and research fellow. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

13 STUDY AUDIT

This study may be selected randomly for audit by NHS Greater Glasgow and Clyde governance team following the annual audit plan.

14 PROTOCOL AMENDMENTS

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the CI following discussion with the TMG and any required amendment forms will be submitted to the REC and sponsor.

The CI will liaise with the study sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and sponsor representative.

Before the amended protocol can be implemented, favourable opinion/approval must be sought from the original reviewing REC, and Research and Development (R&D) office(s).

15 ETHICAL CONSIDERATIONS

15.1 ETHICAL CONDUCT OF THE STUDY

The study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996], Edinburgh [2000], Seoul [2008] and Fortaleza [2013]).

Favourable ethical opinion will be sought from a REC before participants are recruited into this clinical study. Participants will only be allowed to enter the study once they have provided written informed consent or their next of kin have provided written informed assent (if required).

The CI will be responsible for updating the REC of any new information related to the study.

15.2 INFORMED CONSENT

Written informed consent will be obtained from each study participant.

The research nurse or investigator will explain the exact nature of the study in writing, provision of participant information sheet, and verbally. This will include the known side-effects that may be experienced, and the risks of participating in this study. Participants will be informed that they are free to withdraw their consent from the study at any time.

16 INSURANCE AND INDEMNITY

The Pro-BEPP study is sponsored by NHS Greater Glasgow and Clyde. The sponsor will be liable for negligent harm caused by the management of the trial. As employers of the protocol authors, both NHS GG&C and the University of Glasgow will be liable for negligent harm caused by the design of the study. NHS GG&C, as the site of the study, will be responsible for harm caused by the conduct of the study. NHS indemnity is provided under the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS). University of Glasgow clinical trials insurance will apply.

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for clinical negligence and other negligent harm to patients under its duty of care.

17 FUNDING

The study is supported by Versus Arthritis “Probing the Rheumatoid Arthritis Brain to Elucidate Central Pain Pathways ”.

18 ANNUAL REPORTS

Annual progress reports will be submitted to REC on the anniversary of the ethics favourable opinion. A copy of this report will also be sent to the Sponsor.

19 DISSEMINATION OF FINDINGS

In addition to the traditional academic routes of communication and dissemination via peer reviewed publication and national and international conferences, we will also use Research into Inflammatory Arthritis Centre Versus Arthritis (RACE) and Glasgow Arthritis Involvement Network (GAIN) Patient Research Partner (PRP) networks to develop local patient and public involvement (PPI) groups. Supported by Engagement Leads (EL) already in place at each institution, RACE PRPs will form a key part of our communications programme. A PRP member from each institution already attends quarterly centre meetings, accompanied by institutional ELs.

We aim to communicate to the student body in our University via PRP-Student Mentor/Buddy system. Newly appointed PhD students in areas related to this project will be paired with a local PRP volunteer for the duration of their project, ensuring the patient remains at the core of the research and giving the students the opportunity to develop insight and the required skills to communicate their ideas and impact of their work with members of the public.

Local PRP Forum Membership. We will join the local RACE scientific meetings, affording local PRPs the opportunity to interact with the wider RACE community.

Communications support. We will provide lay summaries of the project to the IMID community, as well as contributing to the RACE website. Study Summary results will be available via newsletter. We will ask participants to consent to give their contact details (home /email address) for the purpose of study communication including the dissemination of a newsletter.

20 REFERENCES

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