Study Title: Characterisation of **Pain** in patients with musculoskeletal disease: a prospective, **L**ongitudinal, observational study with an Embedded feasibility window of opportunity **S**leep **S**tudy (PAIN-LESS)

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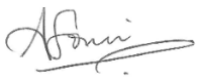
Chief Investigator Signature:	

There are no conflicts of interest to declare.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. SYNOPSIS

Study Title	Characterisation of **Pain** in patients with musculoskeletal disease: a prospective, **L**ongitudinal, observational study with an **E**mbedded feasibility window of opportunity **S**leep **S**tudy (Pain-LESS)	
Internal ref. no. / short title	. Pain-LESS study	
Study Design	Prospective, longitudinal, cohort study with embedded feasibility study of digital CBT-I.	
Study Participants	Patients with musculoskeletal disease	
Planned Sample Size	490 participants with rheumatoid arthritis 490 participants with fibromyalgia (of which 80 will be included in the feasibility study of dCBT-i.	
Planned Study Period	April 15th 2019 to 30th April 2025	
	Objectives	**Outcome Measures**
Primary	To investigate whether patients with inflammatory arthritis and features of centrally driven pain have reduced chance of responding to treatment.	Primary outcome: Percentage achieving Disease Activity Score ≤2.6, 6 months after commencing anti-rheumatic treatment. Secondary outcome: Other measures include Disease Activity Score reduction of ≥1.2; simple disease activity score ≤3.3; Clinical Disease Activity Index ≤2.8; American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Boolean (28 tender joint count, 28 swollen joint count, patient's global assessment (0–10 scale), CRP (mg/dL), all ≤1), modified DAPSA<4.
Secondary	To describe the prevalence of centrally driven pain in patients with other musculoskeletal conditions.	Scoring according to: Central Sensitivity Inventory, Fibromyalgia survey criteria, PainDETECT questionnaire alongside neuroimaging findings.
Secondary	To investigate whether digital CBT-I can improve quality of life and centrally driven symptoms in people with FM To determine barriers and facilitators to a definitive trial of digital CBT-I in people with FM	SIQR, sleep actigraphy, online cognitive assessment at baseline, 12 weeks, and 24 weeks Neuroimaging at baseline and 12 weeks. Focus group at 24 weeks

	To evaluate the cost effectiveness of digital CBT-I	EQ-5D-5L Healthcare usage dairy
Secondary	To investigate whether maladaptive learning in the brain plays a role in chronic musculoskeletal pain, and from this to predict treatment response in fibromyalgia patients	Quantitative Cognitive Testing (online games assessing learning and decision-making, generalisation/avoidance, motor decision-making, and prediction/metacognition tasks). Motor (movement) evaluation - video-based assessment measuring movement during standardised physio-type exercises

2. ABBREVIATIONS

ACR	American College Rheumatology
CBT	Cognitive Behavioural Therapy
CBT-i	Cognitive Behavioural Therapy for insomnia
CDAI	Clinical Disease Activity Index
CI	Chief Investigator
CRF	Case Report Form
CRP	C-reactive protein
CSI	Central Sensitivity Inventory
CWP	Chronic Widespread Pain
DAPSA	Disease Activity index for Psoriatic Arthritis
DAS28	Disease Activity Score 28
dCBT-i	Digital Cognitive Behavioural Therapy for insomnia
EQ-5D-5L	EuroQuol 5-level health questionnaire
EULAR	European League Against Rheumatism
FM	Fibromyalgia
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
HRV	Heart Rate Variability

ICF	Informed Consent Form
ME	Motor (Movement) Evaluation
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NRES	National Research Ethics Service
PDQ	PainDETECT questionnaire
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
PSA	Psoriatic Arthritis
QCAT	Quantitative Cognitive Aversive Testing
QMT	Quantitative Movement Testing
QST	Quantitative Sensory Testing
R&D	NHS Trust R&D Department
RA	Rheumatoid arthritis
REC	Research Ethics Committee
RGEA	Research Governance, Ethics & Assurance, University of Oxford
SIQR	Symptom Impact Questionnaire Revised
SDAI	Simple Disease Activity Score
SOP	Standard Operating Procedure

3. BACKGROUND AND RATIONALE

Musculoskeletal conditions and pain both present huge global health problems (1-3). Pain is estimated to affect 20% of adults overall, with a recognition that such estimates are likely to be conservative due to the lack of a clear definition of pain as a disease entity in its own right (3, 4). Nonetheless, current data show that rheumatoid arthritis, osteoarthritis and spinal problems featuring amongst the leading four causes of pain (3) highlighting the importance of studies focussing on pain as a primary feature of musculoskeletal disease.

Pain in musculoskeletal conditions was traditionally thought to be mostly due to ongoing peripheral nociceptive input, but it is now being recognised that the underlying mechanism of pain is likely to vary between individuals with the same disease category. Previous studies, including work from Professor Tracey's group, have suggested features such as centralised pain and neuropathic pain are related to outcome following knee arthroplasty for primary knee osteoarthritis (5-7). There is also evidence that a central pain component is present in patients with rheumatoid arthritis, for example (8-15). Furthermore the concurrent presence of fibromyalgia and rheumatoid arthritis is common and associated with higher

inflammatory arthritis disease activity scores, worsening of functional status, lower levels of synovial inflammation and more frequent use of biologic therapy (16-20).

Accordingly, treatment selection should theoretically reflect the relative contribution of peripherally and centrally mediated pain pathways in order to personalise therapeutic strategies with the aim of improving response to treatments (21, 22). However, current standard clinical practice does not incorporate this approach to the assessment and management of pain in musculoskeletal disease. The aims of this study are to:

1. To investigate whether patients with inflammatory arthritis and features of centrally driven pain have reduced chance of responding to treatment.
2. To describe the prevalence of centrally driven pain in patients with other musculoskeletal conditions.
3. Establish a cohort of patients who would like to be contacted about likely follow-on studies in the future.

The prospective, observational cohort study will recruit patients being seen in the Oxford University Hospital NHS Trust, or Connect Health (clinical stakeholder organisation with a responsibility to assess and manage patients within the NHS), with a clinical diagnosis of inflammatory arthritis or fibromyalgia. The results will be directly generalisable to patients with these same conditions, who are seen in a secondary care setting. In addition, some aspects may be applicable to patients with the same conditions but who are being managed in primary care.

The study will follow patients as they receive standard treatments being initiated by their clinical care team, who will not be aware of the results of the detailed study pain characterisation. The clinical care of the patient will therefore not be influenced or delayed in any way. The patients participating in the observational study will not benefit directly, but it is anticipated that the results of this study will help to further the goal of personalised patient treatments in the future. As the study does not affect treatment of the patients, the risks of the study are limited to those relating to the study assessment procedures as detailed below in section seven.

Feasibility Study of digital CBT-I

People with FM also commonly suffer from problems with cognition, particularly concentration and memory, and disordered sleep (difficulty getting to sleep, frequent waking in the night or waking early). There are no standard treatments for these centrally driven symptoms. Psychological therapies include cognitive behavioural therapy (CBT), which involves changing unhelpful thought patterns and behaviours. However, in-person CBT is costly and difficult to delivery widely. New forms of CBT have been developed which can be delivered via the internet. These may overcome limitations posed by in-person therapy. A type of CBT for insomnia (CBT-I) has improved cognitive symptoms and disordered sleep in people with insomnia, and may be useful in treating the centrally driven symptoms of FM. CBT-I can be delivered through digital platforms (digital CBT-I, dCBT-I) (26). One such platform is 'Sleepio', a validated dCBT-I tool which has demonstrated efficacy in the treatment of insomnia, and has been shown to alleviate cognitive symptoms of insomnia (27). This programme involves six 20-minute sessions with an animated virtual therapist covering key cognitive and behavioural strategies to improve sleep. We will invite a number of participants to take part in a feasibility study where they will be randomised to Sleepio or standard care. Participants will be evaluated using online assessment tools of pain,

cognition and sleep. In addition, a selection of participants will undergo sleep actigraphy and/or neuroimaging using MRI scans during follow up.

Blood Test

Previous work has shown that patients with fibromyalgia may also have evidence of dermal nerve fibre pathology (23-25). The pathophysiological relevance of this is not clear and it is not known whether these findings relate to the pattern of symptoms a patient have, their pain sensitivity (determined using QST) or their chance of responding well to specific therapies including those used for neuropathic pain. Although it is well recognised that patients with inflammatory arthritis can also develop features consistent with fibromyalgia, potential abnormalities in small unmyelinated nerve fibres has not been studied in this patient population to date. Some patients with peripheral nerve lesions develop neuropathic pain, whereas others do not. It is not currently understood why patients do or do not develop neuropathic pain. Also, some patients' neuropathic pain will improve over time (e.g. with treatment or spontaneously), whereas others will continue to have persistent pain. Currently, it cannot be predicted who will improve and who will continue to have chronic pain. This may relate to factors such as the severity of their neuropathy and the types of nerve fibres involved, psychological factors or genetic predisposition.

Despite the growing evidence for nerve involvement in these pain conditions, its extent and role remains controversial. The presence of a sensitive marker confirming a lesion of the nervous system would increase the certainty of neuropathic pain. Blood based markers of nerve injury have thus gained increasing interest. In particular Neurofilament light chain (NfL) is a consistent diagnostic and prognostic biomarker of central nervous system diseases.

Maladaptive Learning

Despite its prevalence, it is still not fully understood why some people get chronic pain and others do not. One influential idea is that the processes in the brain that normally allow us to adapt to an injury and recover from it, are used excessively, meaning that pain is exaggerated and prolonged beyond what is necessary. This 'maladaptive brain learning' hypothesis, in its various forms, is a popular model of chronic musculoskeletal pain. However, evidence is currently limited by the lack of sufficient tools required to measure and quantify learning. This aspect of the study addresses this by implementing a novel set of online tools based on a basic science understanding of how learning works in the brain. These tools will be used to study outcomes in the fibromyalgia cohort of patients.

The aims of this feasibility study are to:

1. To investigate the feasibility of conducting a study of digital CBT-I in patients living with fibromyalgia
2. To investigate the impact of Sleepio (dCBT-I) on quality of life in people with fibromyalgia.
3. To investigate the impact of Sleepio on centrally driven symptoms including cognition and sleep quality in people with fibromyalgia.
4. To investigate whether patients with features of centrally driven pain have differences in NfL, inflammatory markers and genes which can prospectively identify prognostic factors for developing neuropathic pain, its persistence and/or its severity.
5. To investigate whether maladaptive learning in the brain plays a role in chronic musculoskeletal pain, and from this to predict treatment response in fibromyalgia patients.

In anticipation of likely follow-on and related studies, we will also ask participants if they would like to be added to a research database so that they can be contacted for consideration of any future studies being undertaken by the research group.

4. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective To investigate whether patients with inflammatory arthritis and features of centrally driven pain have reduced chance of responding to treatment.	Percentage achieving Disease Activity Score <2.6. Other measures include Disease Activity Score reduction of >1.2; simple disease activity score <3.3; Clinical Disease Activity Index ≤2.8; American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Boolean (28 tender joint count,28 swollen joint count, patient's global assessment (0–10 scale),CRP (mg/dL), all ≤1), modified DAPSA<4.	Baseline and at 3, 6 and 12 months after commencing therapy.
Secondary Objectives To investigate the features of centrally driven pain, detected through multi-modal assessment, in patients with a range of musculoskeletal conditions.	Scoring according to: Central Sensitivity Inventory, Fibromyalgia survey criteria, PainDETECT questionnaire alongside neuroimaging findings.	Prior to commencing therapy
To investigate whether patients with features of centrally driven pain have differences in NfL, inflammatory markers and genes which can prospectively identify prognostic factors for developing neuropathic pain, its persistence and/or its severity	Blood test	Baseline
To investigate whether digital CBT-I can improve quality of life and centrally driven symptoms in people with FM	SIQR, sleep actigraphy, sleep diary, online cognitive assessment, self-reported cognitive function (British Columbia Cognitive Complaints Inventory, BC-CCI)	Baseline, 12 weeks and 24 weeks
	Neuroimaging (brain MRI)	Baseline and 12 weeks

To investigate the cost effectiveness of digital CBT-I To determine barriers and facilitators to a definitive trial of CBT-I to alleviate symptoms in people with FM To investigate whether maladaptive learning in the brain plays a role in chronic musculoskeletal pain, and from this to predict treatment response in fibromyalgia patients	EQ-5D-5L Healthcare usage dairy Focus groups of participants Online games to include learning and decision-making, generalisation/ avoidance, motor decision-making, and prediction/metacognition tasks, and motor (movement) evaluation - video-based assessment measuring movement during standardised physio-type exercises	Baseline, 12 and 24 weeks 24 weeks Baseline, 12 weeks

5. STUDY DESIGN

This is a prospective, observational, longitudinal study of patients with a range of musculoskeletal conditions being seen in an out-patient setting, with an embedded feasibility study of digital CBT-I.

Participants will be assessed over a 12 month period from receiving new treatment, alongside their routine clinical care. The study assessments will include:

- Confirmation of eligibility to participate in the study (30 minutes) – phone, or in person during routine clinical visit
- Pre-treatment assessment (2 hours) – online questionnaire* and in-person assessment in addition to routine patient care visits
- Follow up assessment at 3 months (2 hours) – online questionnaire* and in-person assessment in addition to routine patient care visits**
- Follow up assessment at 6 and 12 months post-treatment (30 minutes) – online questionnaire*

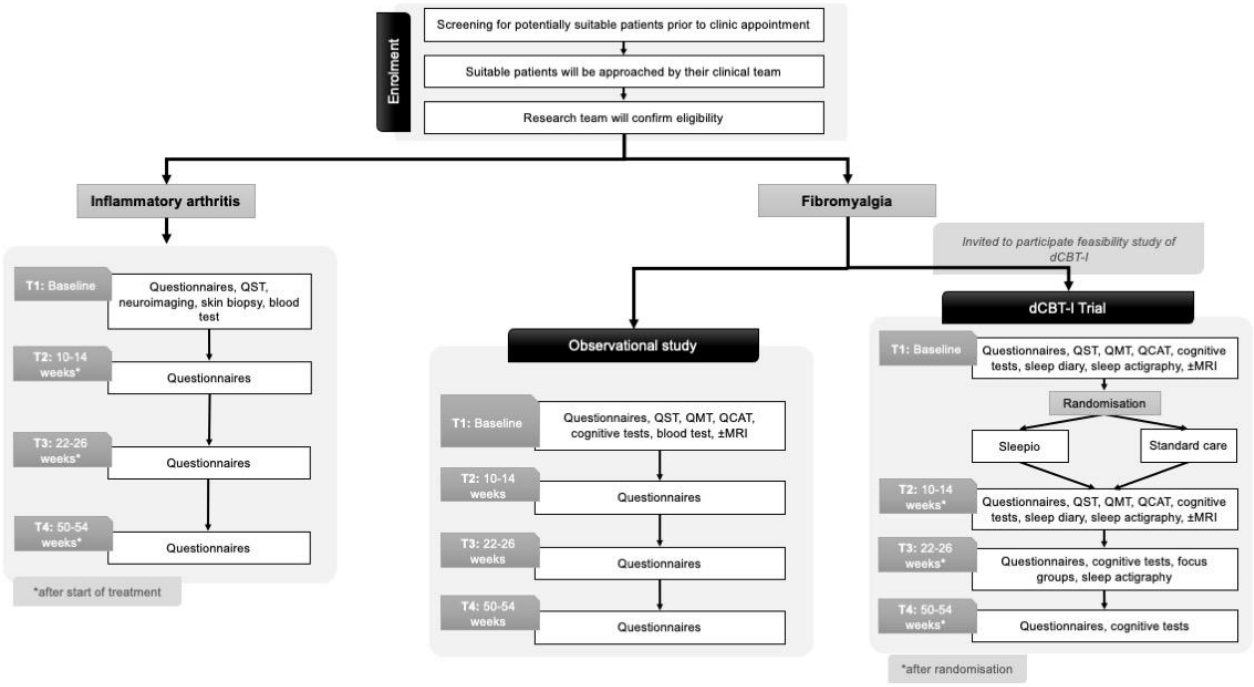
*may be substituted by a shorter telephone administered questionnaire or paper questionnaire if the participant prefers this.

**an additional follow up assessment will be conducted at 1 month in participants receiving treatment with biologic agents. This will be the same as the online questionnaire and in-person assessment being conducted in all participants 3 months after commencing treatment.

If the participant is unable to or does not wish to undertake the MRI component of the main study but is willing to complete the rest of the study, the remainder of the assessment will still be conducted as detailed above.

For participants with fibromyalgia, there is approximately a 6 month wait from clinic assessment/ diagnosis to receiving standard NHS care of pain rehabilitation treatment. Whist waiting for recommended treatment to commence, those with fibromyalgia can choose to also participate in the embedded feasibility study of digital CBT-I, as per the diagram below.

It is estimated that the duration of participant participation in the study will be around 18 months, taking into account the lag between a recommended treatment being commenced. Details of data collection for each assessment are given in sections 7.3 and 7.4 below.



6.0 PARTICIPANT IDENTIFICATION

6.1 Study Participants

Participants with a clinical diagnosis of inflammatory arthritis or fibromyalgia, (fibromyalgia only for the Maladaptive Learning assessments and Sleep sub study), seen as an out-patient within the Oxford University Hospital NHS Trust, or Connect Health (clinical stakeholder organisation with a responsibility to assess and manage patients within the NHS) aged 18 or above will be invited to participate in the study. Clinic lists will be pre-screened for potentially suitable patients by a member of the clinical care team.

6.2 Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.

- Male or Female, aged 18 years or above.
- Clinical diagnosis of either inflammatory arthritis or fibromyalgia/chronic widespread pain

- Feasibility study of digital CBT-I:
    - Concomitant insomnia, frequent waking in the night or early morning waking
    - Self-reported difficulties with concentration or memory
    - Reliable internet access

6.3 Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Patients with a poor understanding of English.
- Patients with known neurological or psychiatric conditions (other than depression or anxiety) likely to independently affect the results of pain assessment, for example peripheral diabetic neuropathy in the opinion of the research team

- Feasibility study of digital CBT-I:
    - Major neuropsychiatric disorder (bipolar disorder, schizophrenia or psychotic spectrum disorders)
        - However, participants with depression and anxiety will be eligible
    - Epilepsy
    - Cognitive impairment, dementia or neurodegenerative disorder
    - Recent or planned surgery
    - Current or planned night-time shift work
    - Sleep disorders such as sleep apnoea, restless leg syndrome, circadian rhythm disorder, or parasomnia
    - Taking prescribed sleep medications on more than 2 nights in past 2 weeks
    - Currently receiving other psychological therapy for insomnia
    - Pregnant or lactating

7 STUDY PROCEDURES

7.1 Recruitment

Potential participants for all sections of the study (Feasibility study included) will be identified via out-patient clinics in the Rheumatology and Pain Relief Unit within the Oxford University NHS Trust, or Connect Health (clinical stakeholder organisations with a responsibility to assess and manage patients within the NHS). Where possible, a member of the clinical care team will pre-screen clinic lists to highlight potentially suitable participants in advance of a clinic appointment. Potential participants will be initially approached by their clinical care team and provided with a participant information leaflet. If the potential participant agrees, the clinician will also pass on the preferred patient contact details to the research team. Posters, with contact details for the research team, will be put up in relevant waiting

areas so that potential participants can ask their clinician about the study and/or contact the research team directly.

The research team will arrange to contact all potential participants, either in person, by email or by telephone, to give them the opportunity to ask any further questions regarding the study. If the participant would like to enrol in the study, the researcher will organise a suitable time for the participant to confirm eligibility for the study, and if suitable take informed consent from the participant.

7.2 Screening and Eligibility Assessment

Screening for all sections of the study (feasibility study included) will involve confirming the participants age, assessment of vulnerability, understanding of English, clinical musculoskeletal diagnosis, and review of the general medical history. Additional MRI safety screening will be conducted in participants willing to undertake the MRI component of the study. This will include questions regarding their suitability to enter an MRI scanner. For the feasibility study additional sleep related screening will be conducted. Screening may be done in person if a participant is attending the hospital for a routine appointment, or by telephone, email or using Microsoft Forms. The participant will be allowed up to one week to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. The restriction of one week is due to the fact that if the patient is due to start on a new treatment, time will be needed to arrange the baseline assessment prior to them starting their new medication. In the case of participants with fibromyalgia who are being referred for pain rehabilitation treatment, there will be more time available, as the waiting time for this is much longer (often up to 6 months). If confirmation of eligibility to participate in the main study and feasibility study is in person, a paper copy of the Participant Information Sheet will be given. If confirmation of eligibility to participate is by phone, a paper copy of the Participant Information Sheet can be posted or emailed. MRI safety screening will be repeated on the day of participation prior to entering the scanner.

7.3 Informed Consent

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed up to one week to consider the information, and have the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. The restriction is due to the fact that if the patient is due to start on a new treatment, time will be needed to arrange the baseline assessment prior to them starting their new medication. In the case of participants with fibromyalgia who are being referred for pain rehabilitation treatment , there will be more time available for the participants to decide, as the waiting time for this is much longer (often up to 6 months). They can choose which of the further assessments they would like to participate in, if at all, whilst they are waiting for their pain management treatment.

Once eligibility and intent to take part in the study have been confirmed by the Chief Investigator or delegated study personnel and the potential participant can personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed, or remote consent can be taken over the telephone by the researcher. The paper consent form or remote consent form will be photocopied and a copy given, emailed or posted to the participant for their own records. The original will be filed in the study site file and another copy scanned into the participant's medical records.

At the point of consent, participants with fibromyalgia can choose to additionally participate in the feasibility study (see section 7.5).

7.4 Baseline Assessments

At the baseline assessment visit, participants will be asked to complete the clinical assessment and validated questionnaires described below. This will be done using REDCap, a secure web application online portal (redcap) where possible, either with the researcher present or independently according the participants preference. If required, a paper format will be used:

Assessment	Purpose
Clinical history	This will include disease duration, current and previous treatments including those for pain management specifically, and other past medical history
Disease activity score measure	Used in routine clinical practice to capture disease activity specific to a condition. For example: disease activity score-28 in rheumatoid arthritis, psoriatic response criteria in psoriatic arthritis, Bath ankylosing spondyloarthritis disease activity index in ankylosing spondyloarthritis, fibromyalgia impact questionnaire in fibromyalgia)
MRI safety questionnaire	Assess whether participant is safe to undergo MRI scanning
Euroqol-5D (EQ5D)/HAQ	Standardised measure of health-related quality of life
Musculoskeletal Health Questionnaire (MSK-HQ)	Supplementary measure of health status designed to be used across a range of musculoskeletal conditions in order to monitor progress over time and response to treatment
Beck depression and anxiety inventories	To assess and describe psychological comorbidity and its impact on symptoms and treatment response
PainDETECT questionnaire	To assess for features of neuropathic pain
Central sensitivity inventory	To indirectly assess centralised sensitisation
Insomnia severity index	To assess sleep disturbance, an important factor in pain experience

Fibromyalgia survey criteria	To assess for concurrent fibromyalgia in those with inflammatory arthritis, which may impact treatment outcome
Fibromyalgia Impact Questionnaire Revised*	To assess the overall impact of symptoms and quality of life in those with FM in Sleep sub-study
Chalder Fatigue Scale*	To assess self-reported fatigue in Sleep sub-study
Behavioural inhibition system/Behavioural activation system (BIS/BAS) scale	To assess reward responsiveness which may be impaired in chronic pain and impact on treatment responsiveness
The Multidimensional Assessment of Interoceptive Awareness (MAIA)	To assess interoception which may be impaired in patients with chronic pain
Locus of control	To quantify the degree to which participant feels they have control over outcome of life events which is likely to be particularly relevant to response to rehabilitation
Credibility Expectancy Questionnaire	To assess expectations of treatment so can adjust for this effect
Tampa scale for kinesophobia	To assess fear of movement which may impact response to treatment
British Columbia Cognitive Complaints Inventory (BC-CCI)*	To assess self-reported cognition in Sleep sub-study
Multiple Ability Self-Report Questionnaire (MASQ) *	This is a measure of self-perceived cognitive difficulties that is more widely used in the fibromyalgia literature to explore subjective cognitive difficulties (i.e. Fibro-fog). The BC-CCI (outlined above) is used in the sleep literature to explore subjective cognitive difficulties. Using both will allow us to compare our results to previous work in both the fibromyalgia and sleep fields
Pittsburgh Sleep Quality Index (PSQI)*	Provides quantitative sleep parameters, such as total sleep time, wake-after-sleep onset
Epworth Sleepiness Scale (ESS)*	A measure of subjective sleepiness
Sleep Disorders Questionnaire*	To screen for sleep disorders which may be an exclusion for participation, such as obstructive sleep apnoea, restless leg syndrome etc (these are already outlined in the exclusion criteria (section 6.3))

* Additional questionnaires if participant consent to the feasibility study

Tasks

Participants will undergo quantitative sensory testing outside the scanner in accordance with the established protocol developed by Rolke and the German Research Group on Neuropathic pain. Quantitative sensory testing is a standard technique used to determine skin sensitivity to thermal, touch, and vibration stimuli. Testing will be conducted over an area which is primarily affected by the musculoskeletal condition of interest (e.g. metacarpophalangeal joints in rheumatoid arthritis), as well as control areas that are not directly involved (e.g. sternum). The exact protocol and test sites will be refined following pilot work in up to 5 participants, in order to ascertain which modalities and test sites

will be practical to assess in this patient population. For those with fibromyalgia, heart rate variability (HRV) will also be measured using the validated Camera HRV app on either the researchers phone or a dedicated device to be used for the study. The participant will hold their index finger to the device camera for 5 minutes and the app will record the HRV. The app was developed by and is owned by a health technology scientist Marco Altini. The camera-based HRV analysis has been validated and used in clinical research and sports training. No personal details are entered into the app - for the purposes of this project, the app simply monitors heart rate for 5 minutes and calculates HRV, providing a value which is documented by the researcher, like any of the other QST instruments. The app is purely a research tool and will have no influence on medical treatment.

Imaging

Participants who are willing and able to take part in the imaging component of the study, will undergo standard brain MRI scans including protocols to image central nervous system structure and function scans, alongside physiological noise monitoring.

Blood Test

Participants will also be invited to have an additional blood sample taken. Blood samples will be assessed for potential biomarkers that can shed a light into mechanisms for the development of neuropathic pain (e.g. cellular, molecular or humoral analysis depending on the type of neuropathy). DNA can show how gene variants may modify the risk of a person developing a neuropathy and/or the severity of neuropathic pain.

Blood sample

The Chief Investigator, or any other trained investigator, will draw max 30mls blood via venepuncture as per the World Health Organisation (WHO) guidelines on drawing blood. The appropriate equipment, including tourniquet, latex/nitrilegloves, vacutainers, sterile needles, cotton wool, alcohol wipes, plasters, clean equipment trays and medical tape will be available in the clinical testing room within the MRI scanning research facility. The room has a comfortable chair for participants with a cushion/pillow/arm rest to support participants' arms while blood is being drawn, and a clinical examination bed where the participant can lie down (with their legs raised if necessary) should they feel faint. Lastly, basic facilities for dealing with participants who faint (or feel faint) during phlebotomy will be provided—somewhere they can lie down and equipment for monitoring blood pressure. There will always be another member of staff in the building whilst this procedure is being performed. There is an appropriate sharps disposal bin in the room. The facility has a needle stick policy in place. The sample will be taken labelled with the participants' ID number. After the participant's appointment, the sample will be taken to the laboratory and will be either processed immediately and/or stored at in a locked freezer at -80 or -20 degrees, in compliance with The Human Tissues Act. Although taking blood is a very standard procedure, common risks are pain during the procedure and bruising (with associated pain afterwards); these will usually disappear within a few days. In the event that a participant reports symptoms of an infection (local redness, swelling, pain or discharge of pus) or other complications, they should be referred to their GP or to A&E urgently.The time required for taking the blood sample is 3 minutes.

Overall, the Baseline Assessment visit will take around 2 hours. Participants will be able to stop at any point and continue after they have had a rest.

Feasibility Study

Recruitment into the feasibility sub-study will be as the procedure described in section 7.1. At the point of consent, participants with fibromyalgia who have chosen to additionally take part in the feasibility study, will be randomised 1:1 to Sleepio or Standard Care, using the Sealed Envelope randomisation software (www.sealedenvelope.com).

The baseline assessment will be the same as for the main study, with a very short QST protocol lasting up to 5 minutes only. In addition, participants will be asked to complete a vigilance task using the study device and the research team will help the participant to capture video data for motor evaluation.

Motor evaluation

Video data of participants doing simple physio exercises, to quantify how they move doing standardised movements. This is done using a smart-phone / tablet camera, which people can set up in their home or attend for a separate study visit. The participant (face included) is recorded doing a list of exercises - marching on the spot holding onto a chair for support, hip and knee extension, squats and heel lifts with chair for support. These typically involve 3 to 4 repetitions and takes a few minutes, after which the video will be uploaded to a secure cloud-server. Motion capture analysis will use inhouse software, owned by the University of Oxford but based on Detectron2 (https://github.com/facebookresearch/detectron2), that allows quantification of movement angles and speeds at different joints, as a metric of physical ability, which can be used to quantify pain related changes in movement; these will be visually inspected for validation. The videos themselves will not be stored but the computer generated skeletal poses will be stored as 2D/3D coordinate time series in pkl or h5 files (see Reconstruction, Figure 1).

Participants will be given information on how to access the maladaptive learning games and cognitive tests, which they can complete at home at their convenience.

Patients will be given an activity watch to wear, and a sleep diary to complete, for 7 days before and after undergoing the Sleepio programme or standard care.

After the visit, participants will then be randomised to standard care or given access to the online CBT-I programme, Sleepio. Participants will be given a web link and activation code to Sleepio. They will be required to complete a daily sleep diary for the duration of the programme. The programme involves six personalised 20-minute video sessions over 10 weeks. It uses evidence-based cognitive and behavioural interventions, sleep hygiene education, and relaxation exercises to target unhelpful behaviours and thoughts in order to reduce symptoms of poor sleep. Participants may use Sleepio in their own time at home via a web browser or smartphone app. Standard care involves provision of written materials produced by the charity Versus Arthritis, with evidence-based advice on sleep hygiene.

Maladaptive Learning

Patients with fibromyalgia can choose to participate in a battery of online learning games that can be played on tablet or smart phone on a separate day. These are validated experimental tasks that probe how people learn and make decisions for rewards (e.g. winning points in a game) and punishments (e.g. losing points in a game). The different games probe different aspects of learning, and each takes around 20 minutes; the score is revealed at the end. The games are as follows:

1i) Balloon popping game (Instrumental learning task). Coloured balloons rise up on the screen, and on each go, participants choose one which balloon they want to pop by touching it on the screen. When a balloon pops it will either give them points, or take away points, or do nothing. Participants can learn which coloured balloons are good and which are bad, but the tricky thing is that this changes continually through the game, so they need to constantly keep track and relearn which ones are good. We analyse in detailed the learning process by looking at people's choices and response times.

ii) 'Road sign check' game (Generalization task). People imagine they are driving through a dangerous mountain road and pass road signs which are symbols on a sign background - the signs mean that it is either safe, or that there is a danger they need to avoid by pressing a button. The problem is that the signs are very similar and can be hard to tell which ones are safety and which are danger signs. Furthermore, you lose points for pressing the 'avoid' button. Therefore you need to look very carefully and only press 'avoid' when you think the sign is a danger sign. The task itself involves a blending of visual features of two exemplar signs, and allows us to assess how people generalise across perceptual space.

iii) Screen touching game (Motor decision-making). Two 'target zones' appear on a screen - a green target, and a red target. If you touch inside the green target you win points, if you touch inside the red, you lose points. The participant needs to touch as quickly as possible, as the targets only appear for a very short time. The problem is that the two targets often overlap, and are often very small, meaning that you need to be both very quick and very accurate - typically trying to touch within the green target that does not overlap with the red, which might only be a slither of the target. We analyse how people's movement actions are affected by the proximity of the red target, given their overall level of accuracy.

iv) Ball balancing game (Motor adaptation). In this game, participants need to hold their phone/tablet horizontally to balance a virtual ball on the screen and stop it rolling off. To make things difficult, there is a constant moving tilt to the screen which they can't see, so they need to concentrate and constantly adjust the way they hold the phone/tablet to stop it rolling off. We analyse how they adjust their movements to different tilts.

v) Prediction games. There are two version of the games: a pain prediction game and a control task, a stockmarket prediction game. In the pain prediction game, participants are required to continuously rate their spontaneous level of pain on a visual analogue scale. Intermittently they will be asked to predict how much pain they expect to feel in the near future, again using another visual analogue scale. Participants are asked to rate the confidence in their estimates. In the control stockmarket task, participants are asked to predict the value of shares changing over time, as in the real-life stockmarket. Again, we will collect confidence ratings for the prediction estimates. The first task evaluates how pain evolves over time, in each subject, and the ability of participants to consciously anticipate pain flare-ups. The control task is used to assess whether there are specific difficulties in anticipating uncertain events involving rewards and losses.

7.5 **Subsequent Visits** – main study

Participants will be followed up at up to four timepoints, as shown in the flowchart in section 5. The questionnaire component can be completed using REDCap, a secure web application, or paper format as preferred by the patient. If the participant is unable to attend for an in-person visit, the questionnaire component of the assessment will be completed either by telephone, using REDCap, or the questionnaires may also be posted to the participant for completion, if this is preferred by the participant. Follow up visits at T2 (10-14 weeks after commencing therapy) and T3 (22-26 weeks after commencing therapy) will be identical, as detailed below:

Follow-up T2 and T3*

The following assessments will be conducted**:

- Repeat eligibility check
- Assessment of disease activity measures and other validated questionnaires listed in baseline assessment
- Update of medical history, medications, and any other therapeutic strategies being used
- QST/brain imaging if conducted at baseline

A further follow-up visit T4 will be conducted at 50-54 weeks after commencing treatment this will include.

The following assessments will be conducted**:

- Repeat eligibility check
- Assessment of disease activity measures and other validated questionnaires listed in baseline assessment
- Update of medical history, medications, and any other therapeutic strategies being used

*In patients with inflammatory arthritis, commencing a biologic therapy, an additional follow up assessment will be conducted at 1 month. This will be identical to the one conducted at follow-up T2 and T3.

**If the participant is unable to attend for an in-person visit, a telephone appointment will be offered in order to complete the questionnaires. The questionnaires may also be posted to the participant for completion, if this is preferred by the participant.

Subsequent Visits – Feasibility study

The follow up at T3 can be conducted remotely. Questionnaires, cognitive testing and maladaptive learning assessments will be completed online and the activity watches will be administered and returned by recorded delivery post. Participants will also be invited by telephone or email to attend a follow up research visit in person, which will be the same as the baseline assessment.

Focus groups

Three groups of 6 participants (18 in total) will be invited to participate in a focus group at T3 (24 weeks). This will be a part of the consent process for this feasibility-study, and participants may opt not to take part. The focus groups will be approximately 3 hours in length, and participants will be reimbursed for their time in accordance with INVOLVE guidelines. These focus groups will be carried out online, using Microsoft Teams, and the recording will be transcribed using MS Teams inbuilt transcription software. Participants in these focus groups will be asked about their views of the study process, with the aim to identify barriers and facilitators to a future definitive trial of the intervention.

7.6 Description of procedure

MRI

Imaging interventions: Once contraindications to magnetic resonance imaging are excluded by use of the facility's screening forms, the risks of undergoing a scan are minimal. A trained scanner operator or radiographer will go through a list of possible risks with the participant before scanning. The MRI scanner consists of a large powerful magnet. Magnetic resonance imaging uses no ionising radiation. There are, however, potential hazards associated with MRI and the scanning of participants including the presence of surgical implants, participants' clothing, jewellery (such as body piercings) bodily habitus, or medical conditions. A comprehensive list of potential risks has been compiled, and the participant should be checked against this by the operator, prior to entering the controlled areas of the MRI scanners. As per standard scanning procedure, participants will be invited to get changed into provided scrubs prior to scanning in order to minimise risk. During the actual scanning procedure, the scanner produces loud banging noises, and the participant will be given suitable hearing protection (earplugs – these will be fitted correctly). The participant will be attached to physiological monitors (i.e. pulse and respiration). Where necessary (i.e. in the case of glasses being removed), vision will be corrected using MR-compatible optical frames. There is a small mirror that will allow them to see out of the scanner. During the experiment, the participant will be able to communicate with the operator in the control room. In addition, they will be given a call button, which allows them to alert the operator at any time. People with a history of claustrophobia may be excluded from participation in the study. All participants will still be introduced carefully to the scanner and allowed to leave at any stage, should they wish to do so. Once in the scanner, participants will be able to indicate immediately if they wish the scanning to cease by pressing a call button in their hands.

Once the participant is comfortable to begin scanning, the radiographer will begin the relevant scan protocol which consists of different MR sequences aimed at imaging different structural and functional properties of the CNS before, during and after the application of different nociceptive stimuli. In some instances, participants will also be presented with innocuous 'control' sensations like visual stimuli (e.g.

flashing chequerboards, colourful images) or auditory stimuli (e.g. white noise) matched in terms of saliency to the painful stimuli.

Immediately following the scan session, the participant will be taken out of the scanner and led to an adjacent, private examination room so that they can change back into their own clothes.

Participants will be thanked and have a follow up visit booked prior to leaving.

The study intervention is online cognitive behavioural therapy for insomnia (CBT-I) through a commercially available programme, Sleepio. The programme involves 6 sessions of automated CBT-I with an automated, virtual professor and access to a daily online sleep diary. Participants may also interact with an online community and library of resources.

7.7 Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of Consent
- Loss to follow up

Withdrawal from the study may result in exclusion of the data from that participant from analysis, if required by the participant.

The sample size for the study takes into account attrition over the course of the study and so withdrawn participants will not need to be directly replaced.

The reason for withdrawal will be recorded in the CRF.

7.8 Definition of End of Study

The end of study is the date of the last postal or online questionnaire/ telephone follow up of the last participant. If the participant has consented to be contacted for consideration of future studies, their name, contact details and musculoskeletal diagnosis will be retained on the research database for a period of 10 years after the end of the study.

8 SAFETY REPORTING

8.1 Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation

- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.2 Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

9 STATISTICS AND ANALYSIS

9.1 Description of Statistical Methods

Non-imaging data will be analysed using statistical software packages such as Stata. Initially descriptive statistics will be used to describe the results of demographic, disease activity and psychophysical assessments conducted across the difference conditions being studied. Statistical approaches used will include chi-squared tests of association, correlation, Student's t-test, and univariable linear regression models. Further analyses will explore whether pre-treatment pain characteristics, in particular the presence of centralises pain, predict response to treatment, measured by reduction in disease activity. This will be done using univariable regression analysis. We will also examine whether there are clusters or sub-groups of patients within the cohort, using data driven methods such as cluster analysis.

All imaging data will be analysed using standard methods within FSL (FMRIB Software Library). The first 5 subjects will be analysed as a first checkpoint to check data quality and other measures of quality. For the maladaptive learning assessments, the results from the online panel of games will be fitted from simulated data, based on pilot studies in patients/controls, for power analysis where parameters of interests will be highlighted with significant differences. The accuracy of model fitting will improve as more data is added i.e. the framework becomes more powerful as more data is added (intrinsic sustainability).

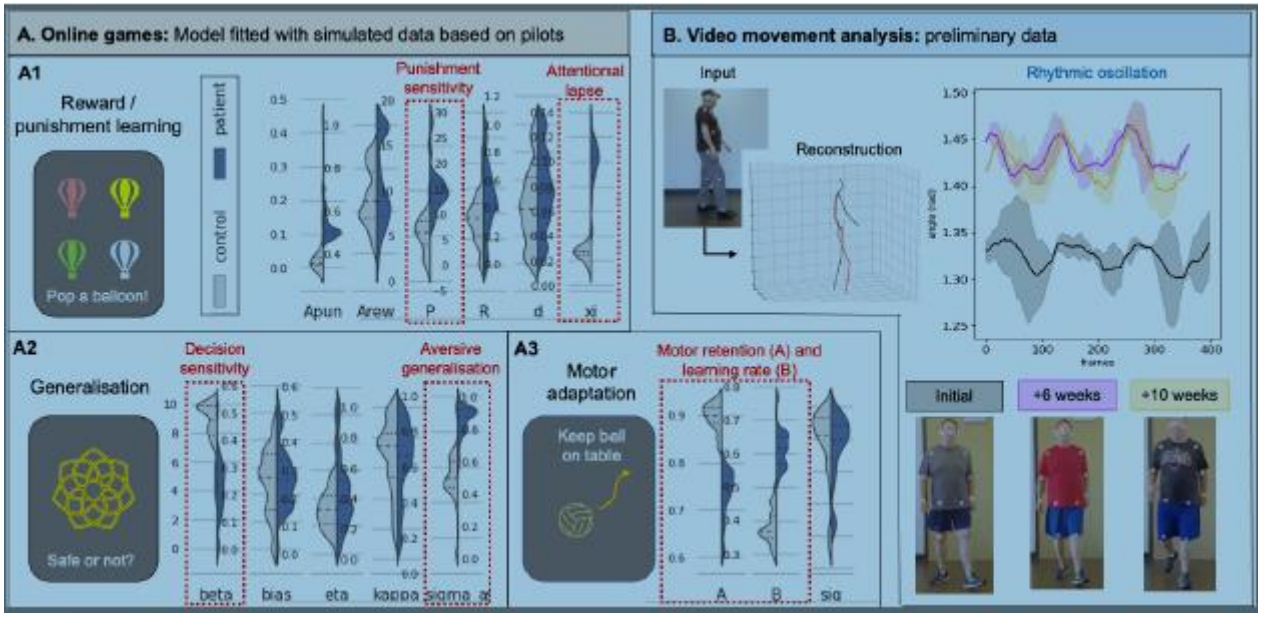


Figure 1. This illustrates what the output data looks like, shown here as the full parameter distributions, but can be simplified to basic summary statistics of the key learning parameters.

For the Sleep sub study, quantitative feasibility outcomes will be summarised descriptively. Qualitative data will be coded using inductive thematic analysis to examine participants' views and experiences of the recruitment process, intervention, and trial process, including MRI assessments. Themes that emerge will be discussed with the patient research partners.

9.2 Number of Participants

Previous work, using the ratio of tender to swollen joints as an indirect marker of central sensitization in patients with either RA or PSA, has shown that on average 43% of patients with low levels of likely central sensitization achieved remission (using DAS-28 remission criteria) compared to 23% in those with high levels of central sensitisation when being treated with either methotrexate or an anti-TNF agent. However a data simulation study showed that, for machine-learning methods, a sample size of 70 times the number of variables allows accurate identification of the data structure (36). Using the seven main variables of pain, fatigue, sleep disturbance, dyscognition, depression, anxiety and function, data for 490 participants, for each condition would be needed, including the feasibility study.

For the feasibility study 80 participants will be recruited in total, with 40 being assessed using MRI. Participants will be randomised on a 1:1 ratio to the intervention and standard care groups. This should provide a large enough sample to inform the practicalities of delivering dCBT-I, MRI assessments, and provide information on recruitment, uptake, and attrition, which will inform the design of the definitive trial. A moderate effect size (Cohen's d >0.3) would be sufficient to accept the result as worth investigating, in order to achieve a meaningful clinical benefit for patients, and in keeping with similar effects of CBT-I on cognitive outcomes in insomnia.

All participants in the Sleep sub-study will be invited to participate in the focus groups. However, it is envisioned that 18 (three groups of six participants) will take part, owing to the time commitment involved.

9.3 Analysis of Outcome Measures

All participant data will be used in the analysis of primary and secondary outcome measures, unless a participant has specified when withdrawing consent that they do not want data already collected to be analysed.

The participants will be divided into those with and without centralised pain, determined by the centralised sensitivity inventory. The difference between achieving remission will be assessed using the standardised DAS -28 criteria at 6 months, in line with the primary outcome measure. Regression analyses will be used to investigate any significant differences in outcome for the two groups, including univariate analyses followed by multivariate analyses adjusting for known predictors of outcome such as age, sex and baseline pain/disease activity severity.

Correlation analyses will be used to assess for any associations between different measures of central sensitization across the different musculoskeletal measures. This will be done for the group as a whole, as well for individual diagnoses to evaluate any differences in the relationships for the different conditions.

10 DATA MANAGEMENT

10.1 Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

10.2 Data Recording and Record Keeping

Data will be collected using REDCap, a secure web-based application, which can be used to directly capture data or in conjunction with paper-based questionnaires where this approach is preferred by the participant. Data will be entered onto an electronic database and stored on a password protected, encrypted University of Oxford computer. REDCap is frequently utilised within the department and there is an established track history in the context of other HRA approved studies. Participant data will be anonymised by allocating an individual reference number. All hard copies of the information will be stored in a locked filing cabinet within swipe and security code access at the Botnar Research Centre.

No personal data needs to be entered onto the Camera HRV app on the study device. The HRV value will be deleted from the device immediately after the value has been recorded on the password protected, secure research database on the university server, using a secured internet connection.

For the Maladaptive Learning component of the study, the videos of participants' movements will be uploaded to a secure cloud server where inhouse software will convert the videos into the computer generated skeletal poses, which will be stored as 2D/3D coordinate time series in pkl or h5 files (see Reconstruction, Figure 1). The original videos will then be deleted.

The Sleepio app collects some identifiable data (such as participants' email address) which is stored on Sleepio's secure servers which researchers will be allowed access to. Sleepio data is stored in data centres, hosted by AWS (Amazon) in the United States. They have HIPAA BAA and EU Model Clause agreements with Amazon, requiring them to adhere to the appropriate EU and US regulations for protecting data. They use consent as their legal basis for processing, and do not generally delete data automatically after a specific amount of time. However, if a user requests a deletion, they will delete within 30 days. All data is encrypted in transit and at rest. Personal data gathered by the Sleepio system is accessible to a limited number of Big Health employees, including members of the engineering & infrastructure, research & clinical, product, commercial, and customer service teams. Any personal data being shared with other organization requires a HIPAA BAA (and EU Model Clauses if appropriate), and requires data to be sent encrypted.

In addition, the online focus groups will be conducted over Microsoft Teams. The Live Transcription feature in Teams will create a transcript of the meeting as it happens. Although the transcription software will use participants' names for identification and accuracy of transcribing, no one at Microsoft ever sees the meeting's content, and the transcripts are automatically deleted immediately after each meeting. Microsoft does not use this data for its own purpose. As no transcription service can be guaranteed to be 100% accurate, the meeting will be recorded. A member of the research team will cross check the transcripts for quality control and the recording will be deleted as soon as transcript verification is complete. Each focus group will be a maximum of 3 hours in length.

11 QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

12.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

12.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA for written approval.

12.4 Reporting

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents. The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

12.5 Participant Confidentiality

The study will comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. All information which is collected about participants during the course of the research will be kept strictly confidential and coded, stored securely under the responsibility of Dr Anushka Soni. Identifiable information will be removed from the information we collect as soon as it is possible to do so. All hard copies of the information will be stored in a locked filing cabinet within swipe and security code access at the Botnar Research Centre. Computerised data will be stored on a password protected, encrypted University of Oxford computer. Data collected via the secured web application will be anonymised at the point of entry to REDCap and stored on a password protected, secured university server at NDORMS: data are collected through a secured internet connection. The information will be stored for a period of 10 years and then will be destroyed securely.

Responsible members of the University of Oxford and the Oxford University Hospital NHS Trust may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

12.6 Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate. In addition, participants in the focus group for the Sleep sub-study for cognitive symptoms will be given a small reimbursement to compensate them for their time. This will be in line with INVOLVE guidance.

12.7 Other Ethical Considerations

Comfort:

i) Certain MRI sequences can be very noisy so subjects will be given earplugs.

ii) The enclosed space of the scanner can induce feelings of claustrophobia. Any subject with a history of claustrophobia will be excluded. Other subjects will be introduced carefully to the scanner and allowed to leave at any stage. Whilst in the scanner subjects have easy access to a call button should they wish to stop the scan or speak with the operator.

iii) Lying on the scanner table for prolonged times can induce lower back pain. This will be minimised by means of comfortable padding and positioning.

iv) Some patients may be asked to delay taking some of their pain related medications, such as paracetamol and non-steroidal anti-inflammatory medications, around the time of the brain scan, as it can affect the results of the MRI. However, this will not preclude a patient from participating in the study if it is not possible to do so.

Ferromagnetic Objects:

Ferromagnetic Objects can be attracted to the scanner and could injure the participant. Magnetic objects in or around the magnet will be tightly secured or MRI compatible in all cases to preclude projectile risks. All researchers entering the magnet environment have undergone annual MRI safety testing to ensure maximal awareness and safety around the scanner and for each research volunteer.

Incidental findings:

In the unlikely event of seeing any structural abnormalities on an MRI scan, the scan will be checked by a clinical specialist. If the specialist feels that the abnormality was medically important, they will discuss the implications with the participant and arrange for further investigations as necessary. Participants will not be informed unless the specialist considers the finding has clear implications for their current or future health. It is important to note that scans are not carried out for diagnostic purposes, and therefore the scans are not a substitute for a clinical appointment. Rather, the scans are intended for research purposes only.

It is known that some inherited genes increase the risk of certain health conditions, for instance heart disease or rare forms of cancer. In people whose risk is known to be higher than average, medical action may be taken to reduce the risk of these conditions developing or causing problems in the future. From the blood samples and skin biopsies collected for the sub study, it is possible that genetic changes may be found by chance (incidental findings), which may increase the risk of the individual developing one of these conditions. Each participant can decide on the consent form whether or not they want to be informed about such medically actionable findings. If a medically actionable finding is identified and the participant opted to be informed, then a clinically qualified member of the research team will arrange an appointment with the participant to discuss the findings.

Experimental pain stimuli:

All stimuli that are used to experimentally induce pain have been safely used as part of our pain research programme in ethically approved projects (see IDREC Approved Protocol 19, v4 "**STUDIES INVESTIGATING EXPERIMENTALLY INDUCED PAIN IN ADULT HEALTHY VOLUNTEERS**"). The minimal intensity of noxious stimuli necessary to achieve goals of the study is established. The stimulation intensity does not exceed the individual tolerance level. Participants are always able to terminate a painful stimulus at will. The exact test paradigm will be optimised through a period of pilot work in and outside the scanner in order to best mimic the clinical pain being experienced.

1. Mechanical Stimuli:

Sensation-related touch, including a sharp pinprick, can be elicited using Von Frey hairs and punctuate stimuli specifically designed to deliver a constant force to the skin surface. Vibration can also be delivered using specially designed Vibro-Tactile pads on the surface of the skin. None of these devices penetrate the skin. The maximum force delivered will be 512 mN for punctate probes.

2. Thermal Stimuli:

Thermal stimulations including hot and cold sensations can be elicited using thermode devices specifically designed to deliver thermal sensations to the skin surface. Thermal temperature can also be maintained or modulated by the use of warm/cold compresses (e.g. water bottles) that can be placed on the surface of the skin. The absolute temperature range delivered will be between 0 and 55 degrees Celsius (see IDREC Approved Protocol 19, v4 "**STUDIES INVESTIGATING EXPERIMENTALLY INDUCED PAIN IN ADULT HEALTHY VOLUNTEERS**").

There are no known side effects to any of these stimulations. These have been approved in earlier NHS ethics applications for use in the FMRIB pain laboratory and can be used in conjuncture with one another and in MR environments (see Approved Protocol 19).

The Sleep sub-study does not pose any ethical concerns relating to the intervention, Sleepio. Participants will be randomised to a standard care control, and their usual care will not be influenced or delayed in any way. Sleepio is an online NICE-accredited cognitive behavioural therapy for insomnia tool, which has previously been validated as effective and safe in insomnia. The use of Sleepio poses minimal risks to participants.

13 FINANCE AND INSURANCE

13.1 Funding

The study is fully funded by the Oxford-UCB prize fellowship.

13.2 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

14 PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the Oxford-UCB Prize Fellowship. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

15 INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The protection and exploitation of any new IP is managed by the University's technology transfer office, Oxford University Innovations.

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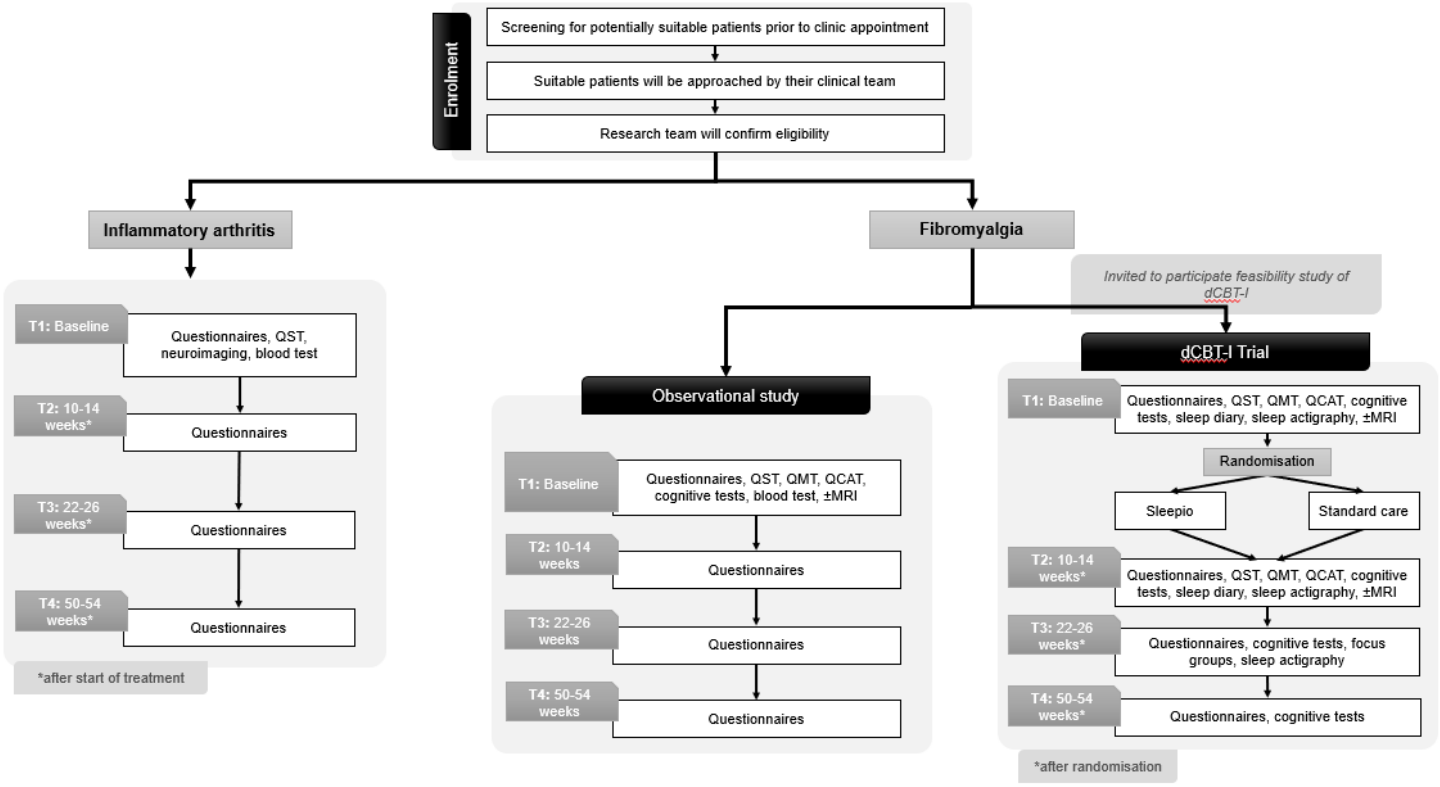
17 APPENDIX A: STUDY FLOW CHART



APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2	7th October 2020	Dr Anushka Soni	Inclusion of sub-study (blood test and skin biopsy), updated PIL and electronic consent form
2	3	10th January 2022	Dr Anushka Soni	Additional investigators; amendment of planned study size from 200 to 490; extension of planned study end date to 30 April 2025; inclusion of Maladaptive Learning assessments within main study and Sleep sub-study, updated consent forms, PIL and separate Sleep study consent form and PIL
3	4	23 September 2022	Dr Anushka Soni	Clarification of planned sample size. Additional movement analysis for the Maladaptive

				Learning assessments, recruitment from Connect Health, updated outcome measure questionnaires for Sleep sub-study, updated study flowchart, new study documents - remote consent forms, research invitation letter, maladaptive learning sub study email.
4	5	07 February 2023	Dr Anushka Soni	Updated study name. Amendment of sample size from 100 to 80 for those with fibromyalgia. Sleep Disorders Questionnaire administered via email or Microsoft Forms for fibromyalgia sleep screening. Addition of the British Colombia Cognitive Complaints Inventory, EQ-5D-5L and healthcare useage questions added to REDCap. Option to record heart rate variability on an ipad. Simplification and alignment of study arms for fibromyalgia, including: renaming sleep sub-study as a feasibility study; reordering of paragraphs in protocol for clarity, rewording of secondary objectives of study, removal of skin biopsy from study protocol and associated documents, incorporation of the seperate sleep sub-study Patient Information Sheet and Consent Forms into main study documentation and updated study flow diagram. Addition of Sleepio instructions and paper copy of sleep diary. Study posters for clinicians and patients. Removal of Healthshare from Participating Organisations. Revised inclusion criteria and removal of option of MS Forms Consent Form.