

# Identifying subgroups within a population of chronic non-specific low back pain sufferers, and investigating the role of the immune system in certain subgroups by considering their relationship to chronic primary pain syndromes

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<b>Registration date</b> 23/06/2021	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 12/07/2021	<b>Condition category</b> Musculoskeletal Diseases	<input type="checkbox"/> Individual participant data <input type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

Non-Specific Low Back Pain (NsLBP) is back pain that does not have an identifiable cause, and will affect around 8 out of 10 people during their lifetime. For some this pain can be significant and long-term, affecting their quality of life, financial circumstances and social interactions. Despite the large number of NsLBP sufferers, we still do not yet fully understand the causes and risks associated with the development of this pain. Current treatment can be beneficial for some but many are left without appropriate symptom control.

Recent research from our group has identified the importance of immune factors in the chronic painful conditions of Complex Regional Pain Syndrome (CRPS – a pain condition that may develop after trauma in a limb) and Fibromyalgia (a widespread pain condition). These conditions are associated with severe pain on light touch/pressure and local skin signs such as increased sweating, or with widespread pain.

Some patients with severe NsLBP present with similar skin signs to CRPS, and NsLBP is a risk factor for the development of Fibromyalgia. We wish to find out whether a specific group of NsLBP sufferers may have similar signs and immune changes as those with CRPS and if sufferers can be identified early as being at particularly high risk for the development of Fibromyalgia. In addition, we wonder whether individuals who may suffer from immune-related pain share similar personal characteristics, such as pain scores or coping mechanisms. This study will provide blood samples for investigations into immune factors and cells, including their function and character related to pain, as well as analysis of DNA for genetic links.

We expect that this study will allow us, for the first time, to identify subgroups of NsLBP with similar immune abnormalities to CRPS or Fibromyalgia, opening new avenues for their future treatment.

### Who can participate?

Patients 18 years or older with non-specific LBP without the presence of another condition to explain the pain

### What does the study involve?

Participants will be identified at routine physiotherapy appointments, or from previous registration on a local Pain Registry. They will be asked to contact the study team to arrange an initial meeting to discuss involvement in the study. Participants will be asked to complete a series of questionnaires around mental health, social circumstances and pain symptoms prior to attending for the first study visit. At this visit each participant will undergo a routine examination of the lower back and limbs, as well as an assessment of any excess sweating at the back. Tests looking at the sensitivity of the skin at the lower back and arm will be performed, and samples of blood will be taken, up to a maximum of 12 tablespoons, for storage and analysis into immune function and molecules related to pain. These samples will also be used for later DNA analysis into specific genes related to pain.

Ten participants with severe changes in skin sensitivity at the lower back may be invited back for a second study visit, where they will have small blisters formed on the skin of their lower back and arm. These are painless and do not scar. The blister fluid will be analysed for changes in immune function. Another sample of blood will also be taken.

Thirty participants who present with low back pain occurring in worsening 'flares' will also be invited back for an additional visit at a time of worsening pain, when they will be re-examined and have another sample of blood taken.

Finally, one year after the first visit, participants will be followed up via telephone and complete a remote questionnaire. In participants who report symptoms of widespread pains we may invite them to return for a further visit to assess the development of Fibromyalgia and take another blood sample.

No participant will be asked to attend every one of the visits mentioned.

### What are the possible benefits and risks of participating?

There are no immediate direct benefits to those taking part. However, we hope in the future that the information we discover can be used to improve the lives of everyone with non-specific low back pain. Participants will be asked to donate a sample of blood during the study visit. Blood donation carries a minimal risk related to skin and muscle trauma. All steps will be taken to ensure participant safety and the blood will be taken only by a registered healthcare practitioner. The formation of skin blisters is not a painful procedure, but there is a rare risk of delayed healing of the blister sites and irritation at the site. In the extremely unlikely event that any issues arise we will contact the participants' GP, with their consent, and they will arrange the necessary follow-up.

### Where is the study run from?

University of Liverpool (UK)

### When is the study starting and how long is it expected to run for?

January 2019 to December 2023

### Who is funding the study?

Pain Relief Foundation (UK)

### Who is the main contact?

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## Contact information

### Type(s)

Scientific

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## Additional identifiers

### Clinical Trials Information System (CTIS)

Nil known

### Protocol serial number

CPMS 48956

## Study information

### Scientific Title

Autoimmunity-informed phenotyping in chronic non-specific low-back pain

## **Study objectives**

There will be distinct subgroups within the study population, who suffer from chronic non-specific low back pain, identifiable through their reported and measured characteristics. Some of these subgroups will show signs and symptoms associated with the pain syndromes of Complex Regional Pain Syndrome (CRPS) and Fibromyalgia (FMS), and that dysregulation of the immune system will play a role in these subgroups.

## **Ethics approval required**

Old ethics approval format

## **Ethics approval(s)**

Approved 10/06/2021, Wales REC 7 (Public Health Wales Meeting Room, Building 1, St. David's Park, Carmarthen, SA31 3HB, UK; +44 (0)2920 230457; Wales.REC7@wales.nhs.uk), ref: 21/WA/0120

## **Study design**

Observational cohort study

## **Primary study design**

Observational

## **Study type(s)**

Diagnostic

## **Health condition(s) or problem(s) studied**

Non-specific low back pain

## **Interventions**

We will identify 100 patients from back pain physiotherapist clinics run at the Walton Centre and Aintree Hospital in Liverpool, UK. We have chosen to recruit 100 individuals based on evidence from previous exploratory studies showing that this number is sufficient to allow subgroup identification within a population and appropriate analysis of the genetic basis of extreme pain. Physiotherapists will identify patients with non-specific low back pain who would meet the inclusion criteria of the study. They will inform the patient briefly of the study and provide an information leaflet with contact details to arrange participation. Individuals with back pain may also be identified as potential participants from the Walton Clinical Pain Management Registry and be informed of the study. Individuals will contact the study team to register interest and arrange a study visit.

Interested individuals will arrange a video meeting with the study team, to reduce COVID transmission risks, during which suitability for the study will be assessed, the study will be explained and informed consent taken. Following consent, the study team will arrange a study visit and mail or email a series of questionnaires aimed at measuring the levels of known factors related to low back pain, such as depressive symptoms and stress levels, to be completed by each participant and returned at the first study visit. Participants will be seen in the laboratories of the Pain Research Institute where they will then be examined with a focus on non-specific low back pain. The participant will be asked to identify the most painful area at the lower back and this will be examined for evidence of tissue swelling. Quantitative Sensory Testing (QST) uses a number of special tests to investigate the sensory profile of certain nerve fibres and can identify abnormal functioning in these nerves. The use of QST in CRPS, FMS and LBP is well documented and can be used to either support diagnosis of the condition, as in CRPS, or identify subgroups

of patients with altered nerve functioning, as in LBP. The full, validated DFNS protocol will be performed on each patient, with the area of maximal pain at the lower back used as the test site and the forearm used as a control site. We will also use a starch-iodine solution which, when applied to the skin, changes colour based on the degree of sweating at that site. Sweating is a feature of CRPS and we wonder whether a subgroup of LBP sufferers present with this as well.

We will take sample of blood from each participant and store this for later analysis of immune factors. It is estimated that each visit will require a total of around 2-3 hours. Patient travel and time will be reimbursed to a maximum of £30 per visit.

Within this initial group of 100 participants we will identify 10 participants with the most severe CRPS-like symptoms and invite them back for a single further visit, at a time when their back pain is severe. However if the participant reports that the pain could not get any worse or that they would be unwilling to return during an acute flare due to pain/functional limitation, and they are deemed suitable for a second-visit, the sampling of blister fluid may be conducted at the first study visit. We will use a small device to create painless blisters on the skin over the painful areas and take a small sample of fluid from these blisters for analysis of immune factors. We will take another sample of blood, ideally at a similar time to the first visit, for later analysis of immune factors.

We will also invite 30 participants who do not present with CRPS-like features for a second visit, this time during a pain flare, for blood sampling and storage for analysis. This will allow for comparison with the CRPS-like group to identify important differences in serum factors.

Contact details of those taking part will be kept for one year after involvement in the study and at the end of this year we will arrange a telephone interview to assess the course of pain and any change in symptoms, with particular interest in the development of chronic widespread pain and fibromyalgia (FMS) symptoms. Those people that report these symptoms will be invited back for a final visit where they will be examined with a focus on FMS features, and a final sample of blood taken for later analysis of immune factors. Participants who had been included in the blister-fluid sample population will not be invited back for further consideration in this CWP /FMS population.

Data analysis and interpretation will be performed during the study and following completion of the last visit.

## **Intervention Type**

Other

## **Primary outcome(s)**

Participant characteristics, as measured by questionnaire responses and clinical examination findings at baseline:

1. Age and Gender
2. Ethnicity
3. BMI (kg/m<sup>2</sup>)
4. Past Medical History
5. Past and Current Medications
6. Pain Duration (months)
7. Average Income
8. Highest Educational level achieved
9. Depression severity and risk
10. Markers of life stress exposure

11. Clinical course of pain
12. Tissue swelling in low back pain
13. Alcohol and smoking use
14. Waddell Score
15. Suction blister fluid cytokine levels
16. Anatomical location of most severe pain
17. Presence of widespread, secondary pain
18. Presence and degree of sweating at lower back
19. QST profiles

#### Questionnaires

1. Present Pain Intensity (0-10 scale)
2. Hospital Anxiety and Depression Scale (HADS)
3. Keele STarT back screening tool
4. Brief Pain Inventory
5. Short-Form McGill Pain Questionnaire
6. Coping Strategies Questionnaire
7. Pain Self-Efficacy Questionnaire
8. Daily Stressors Questionnaire
9. EQ-5D
10. painDETECT Questionnaire
11. Revised Illness Perception Questionnaire (IPQ-R) – timeline questions
12. Touch Experiences and Attitudes Questionnaire (TEAQ)

#### Key secondary outcome(s)

1. Somatosensory profiles, as measured by quantitative sensory testing, at baseline
2. Presence of bilateral tissue oedema at the lower back on visual assessment at baseline
3. Presence of excess sweating at the lower back, as measured using the Modified Minors Starch Iodine test at baseline
4. Anatomical site of maximum pain at the lower back, as measured using the painDETECT questionnaire at baseline
5. Local immune mediator levels in non-specific low back pain patients with a CRPS-like presentation, as measured by ELISA analysis at baseline
6. Conversion rate from localised non-specific low back pain to FMS, as measured by the American College of Rheumatology Fibromyalgia criteria, at 12-month follow-up

#### Completion date

01/12/2023

## Eligibility

#### Key inclusion criteria

1. 18 years or older
2. Presence of non-specific LBP without the presence of another condition to explain the pain (ie. cancer, primary musculoskeletal conditions, sciatica)
3. Chronic NsLBP defined as pain persisting for >12 weeks, with pain occurring >4 days/week
4. Non-specific LBP as defined topographically and temporally by the Delphi definition
5. Average weekly pain intensity exceeding 6/10 on VAS scoring
6. LBP that causes severe disability, as defined by the Modified Oswestry Low Back Pain Disability Questionnaire (MODI)
7. Pain may radiate down the buttocks or backs of legs but must not radiate below the knees

8. In patients with features of more widespread, non-specific pain, the low-back pain must be the predominant complaint of pain and the pain intensity of these other pains should not exceed 3 /10 on VAS scoring

**Participant type(s)**

Patient

**Healthy volunteers allowed**

No

**Age group**

Adult

**Lower age limit**

18 years

**Sex**

All

**Key exclusion criteria**

1. Pregnant or breastfeeding patients
2. Patients with immune deficiency or taking immune modulating drugs
3. Patients with an acute systemic disorder
4. Language other than English as first language

**Date of first enrolment**

01/08/2021

**Date of final enrolment**

01/07/2022

**Locations**

**Countries of recruitment**

United Kingdom

England

**Study participating centre**

**Aintree University Hospital**

Lower Lane

Liverpool

United Kingdom

L9 7AL

**Study participating centre**

**The Walton Centre NHS Foundation Trust**  
Lower Lane  
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## Sponsor information

### Organisation

University of Liverpool

### ROR

<https://ror.org/04xs57h96>

## Funder(s)

### Funder type

Charity

### Funder Name

Pain Relief Foundation

### Alternative Name(s)

The Pain Relief Foundation

### Funding Body Type

Private sector organisation

### Funding Body Subtype

Trusts, charities, foundations (both public and private)

### Location

United Kingdom

## Results and Publications

### Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request. [andreasgoebel@rocketmail.com](mailto:andreasgoebel@rocketmail.com)

- Raw data, with patient identification details removed, will be made available.
- Data will be made available immediately following publication and for 10 years following the study, as per University of Liverpool policy.

- Data will be available to investigators who provide methodologically sound and ethically approved proposals.
- All analysis types will be considered on an individual basis.
- Consent from participants will be obtained during the initial study consent process.
- Data will be anonymised, with all identifying patient details removed.

## IPD sharing plan summary

Available on request

### Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">HRA research summary</a>			28/06/2023	No	No
<a href="#">Participant information sheet</a>	version V2.0		23/06/2021	No	Yes
<a href="#">Protocol file</a>	version V3.0	27/05/2021	23/06/2021	No	No