Pain Centre Versus Arthritis

Annual Report 2024

Executive Committee: David Andrew Walsh and Victoria Chapman (Co-Directors), Federico- Dajas-Bailador, Eamonn Ferguson, Duncan Hodkinson, Roger Knaggs, Weiya Zhang

Period of Review: May 2023 – March 2024

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PAIN CENTRE VERSUS ARTHRITIS at the University of Nottingham

Contents

Mission

Pain Centre Versus Arthritis pursues international excellence in multidisciplinary, translational research, thereby enhancing understanding of pain and improving its treatment.

Introduction from the co-directors

Pain Centre Versus Arthritis is a collaborative community of outstanding, multidisciplinary researchers with strong national and international links. Each year we contribute to the worldwide advances in chronic pain research, moving one step closer to fully understanding the mechanisms of pain.To achieve this, our scientists address pain from the standpoint of multiple disciplines - neuroscience, orthopaedics, rheumatology, psychology,genetics, molecular biology and evidence-based medicine. At the core of all our research are people with lived experience of pain. We embrace partnerships with external user groups, charities, industry and academic institutions, in both the UK and across the world. This report highlights our world-class research outputs.

This year's achievements are especially notable in fundamental science, treatment efficacy and real-world evidence research. We have pushed forward understanding of endogenous analgesic pathways, both bioactive lipids and opioids, to better harness them to reduce musculoskeletal pain. We have developed new and improved ways to detect and measure nociplasticity, including our Central Aspects of Pain questionnaire, dynamic and static modalities of quantitative sensory testing, and brain connectivity detected by fMRI. We've used biomarkers and assessment tools to find more effective pharmacological and non-pharmacological methods to relieve pain. Our expertise in real world and evidence-based medicine has drawn attention to the unacceptable burdens of musculoskeletal pain, and contributed to classification criteria and guidelines for its diagnosis and management.

We are growing a future generation of world class scientists in pain research by providing unparalleled training and educational opportunities to our PhD students and early career researchers through teaching, handson research practice and multidisciplinary discussion.

The story so far

Pain Centre Versus Arthritis opened in 2010 and developed into an internationally esteemed and multidisciplinary research centre with strong national, international, charity and industry ties. The primary objective of the Centre remains to enhance understanding of chronic pain and turn

new therapeutic approaches into reality. Our over-riding ambition is to improve the quality of life for those living with pain.

The multidisciplinary and translational strategy of Pain Centre Versus Arthritis has continued to sustain a high volume of novel research outputs.

We continue to build upon our cohorts and biorepositories. Knee Pain and related health In the Community (KPIC) collates longitudinal data including pandemic/lockdown measures from populations with or without chronic pain. Another cohort, the Investigating Musculoskeletal Health and Wellbeing survey (IMH&W), provides further important information about people with or at risk of developing arthritis or other musculoskeletal diseases, or frailty. Together, KPIC and IMH&W include information from more than 1,500 individuals, provided at several time points over several years. They help us understand what the key factors are that predict whether pain will go away, persist or get worse, including genes and chemicals in our bodies, medical conditions, things we do, treatments that we take, and external factors such as the covid-19 pandemic. They inform recruitment of participants to clinical research projects. Furthermore, our biorepositories, such as Joint Tissue Repository, provide access for the research community to blood, joint fluids and tissues that have been donated by people who have or do not have arthritis. We have been using these samples to identify and measure molecules (RNA, proteins, biolipids) that might cause knee pain, and to discover new medications that might relieve that pain.

We have extended our laboratory research to identify and develop models that mimic the mechanisms of human pain, in order to explore in more detail the molecular and electrophysiological mechanisms through which joints can become painful. These include complex models of disease, and cellular models for exploring how nerves grow and respond to their environment. We have used these models to explore novel medical approaches such as knocking down protein expression using siRNAs, and interfering with lipid metabolism in ways that can shift the balance from increasing to decreasing, or even switching off pain.

We have further developed ways of assessing pain, in both people and our models, in order to better understand pain's underlying mechanisms in the individual. Our Central Aspects of Pain in the knee (CAP-Knee) questionnaire measures symptoms that are associated with the increased sensitivity that occurs in people with chronic pain, and has been used to measure this central aspect of pain in a wide range of painful musculoskeletal conditions, including osteoarthritis, low back pain, fibromyalgia and rheumatoid arthritis. We have demonstrated that

mechanisms and psychological aspects of pain driven by the Central Nervous System may be shared between a wide range of painful musculoskeletal conditions. Our refinement of methods such as QuantitativeSensory Testing (QST) to measure pain sensitivity driven by the central nervous system has been used to understand similarities and differences between a wide range of musculoskeletal diagnoses. Our QST protocols have been adopted by the Advanced Pain Discovery Platform as standards across the UK for assessing central sensitisation in musculoskeletal conditions.

Our research on functional changes within the brain in people with painful osteoarthritis has led to our completion of a mechanistic clinical trial using Transcranial Magnetic Stimulation (TMS). Through this we aimed to reverse abnormalities in brain connectivity in order to reduce pain in people with osteoarthritis. The TMS intervention was well tolerated by patients, and the complex data from the trial are being analysed.

Collaborations

The Pain Centre continues to collaborate with those working in the field of pain research nationally and internationally, in order to pursue multidisciplinary, relevant research into the better understanding and treatment of chronic pain. Professor Walsh is Programme Director of Advanced Pain Discovery Platform (APDP). Collaborations take the form of sharing of research expertise, training, data and biosamples.

We currently have active UK collaborations across the UK, including:

Academic institutions; Cardiff, Keele and Loughborough Universities, and Universities of Bristol,Hertfordshire, Manchester, Manchester Metropolitan, Oxford, Sheffield, London (King's and University Colleges, St George's Hospital) London, Warwick, Exeter, Aberdeen and the West of England.

Clinical service providers: Nottingham University Hospitals, Sherwood Forest Hospitals and University Hospitals of Derby and Burton NHS Foundation Trusts, West Suffolk Hospital, Llandough, North Bristol, St Bartholomew's (London), York, and Royal Devon and Exeter Hospitals NHS Trusts, Nottingham CityCare Partnership.

NIHR clinical research organisations: Nottingham, Birmingham and Bristol Biomedical Research Centres, Applied Research Collaboration-East Midlands, Leicester, UK.

Our *international collaborations* currently include:

Europe	
Belgium	• Centre for Environment & Health • Research Foundation-Flanders (FWO) • University of Leuven • Vrije Universiteit Brussel
Canada	• University of Saskatchewan
Denmark	• Aalborg University
France	• Hôpital Ambroise Paré • University Hospital Clermont-Ferrand • Descartes University
Germany	• University of Heidelberg • Max Planck Institute of Psychiatry
Norway	• SINTEF, Trondheim
Spain	• Universidad Rey Juan Carlson
Sweden	• Lund University • University of Gothenburg
Switzerland	• University Hospital Lausanne • Zurzach Care Group
The Netherlands	• Erasmus MC • Leiden University
Rest of the World	
Brazil	• São Paulo State University
Japan	• Niigata University
Malaysia	• University of Malaya, Kuala Lumpur
Saudi Arabia	• Taif University • King Abdul Aziz University
United States of America	• Boston University • PRIDE Research Foundation • Cornell University • University of California • University of Texas • Harvard University • Wake Forest School of Medicine
Uruguay	• IIBCE Institute, Montevideo
China	• Jiaxing University • Central South China University, Changsha
Taiwan	• Chang Gung Memorial Hospital
Turkey	• Sağlık Bilimleri Üniversitesi
Australia	• The University of Sydney • Monash University • Adelaide University

Training, Capacity Building and Educational Activities:

Pain Centre Meetings

We offer diverse meetings to our Pain Centre membership. Each has a distinct focus, however the fundamental aim is to bring the community of researchers together, increase awareness of the research that is being done, and to contribute to the training of students and early career researchers.

Internal Scientific Meetings allow Pain Centre members to present their research to both preclinical and clinical scientists. The research presented may be at any stage from development to conclusion. The meetings provide an opportunity for presenters to take on board useful input from others. Members may present on the same research more than once, as their project progresses. For students, these meetings are also an important opportunity to gain confidence in presenting and responding to questions.

Preclinical Meetings allow for the presentation and discussion of mechanistic pain research progress.

External Scientific Meetings allow Pain Centre members, and members of the public, to listen to an invited external speaker. These meetings serve to extend the reach of the Pain Centre and provide networking opportunities beyond its membership. The Pain Centre also hosted the 2nd Annual Advanced Pain Discovery Platform conference bringing its members into contact with world leaders in pain research from around the UK.

For a list of Pain Centre meetings, please visit the following link.

During the period of this report, Pain Centre members have provided workshops and presentations to national and international conferences including British Pain Society (Glasgow), EULAR (Milan), HEAL (USA virtual meeting), EFIC (Budapest), American College of Rheumatology (San Diego, USA), Faculty of Pain Medicine (London), C-COMP (Chicago), Blast and Conflict Injury Conference (London), SOPATE (Brussels) and OARSI (Vienna).

Teaching Activities

The Pain Centre membership offers diverse cross-disciplinary expertise in the fields of neuroscience, rheumatology, orthopaedics, molecular biology, psychology, pharmacy, mathematics, physics, life sciences, animal sciences, health sciences, imaging, sport and exercise medicine – amongst others.

Practising clinicians and academic members of the Pain Centre deliver

lectures at undergraduate and postgraduate level, including supervision of PhD students. Members have teaching specialties in subjects such as: Neuroscience (Tobias Bast, Gareth Hathway, Federico Dajas-Bailador, Victoria Chapman), mental health, public health (Holly Blake), opioids (Roger Knaggs), health psychology (Eamonn Ferguson, Holly Blake), biopharmaceutics (Pavel Gershkovich), physiotherapy (Michelle Hall, Vasileios Georgopoulos), physiology (John Harris), physical activity and exercise in pain management (Paul Hendrick), health economy (Marilyn James), cross-cultural health care (Joe Kai), pain management (Roger Knaggs, David Walsh), patient and public involvement in research (Joanne Stocks).

In training our cohorts of PhD students, the focus is on establishing sound knowledge and robust understanding, which students have the confidence to present, whilst ensuring that outcomes are applicable and useful from a patient perspective.

Public and Patient Involvement and Engagement (PPIE)

The Centre's Patient and Public Involvement Advisory Group (PPAG) is hosted by the Pain Centre. The group enables the input and involvement of people with lived experience of pain to be central to shaping pain research design. The PPAG and its members help ensure that our research outcomes are actionable and are more likely to be of benefit to those with lived experience, and that information shared by academic pain researchers is truly accessible to a lay audience. We encourage academic researchers to engage with the PPAG, and we provide guidance to early career researchers on the use of PPIE in their research as needed.

We have had well in excess of 100 individual instances of involvement from members of our PPAG, across a number of studies or projects, in the last year. Examples of activities that PPAG members have been involved in have included:

- inputting into lay summaries of grant applications (on pain and frailty, and inflammation-induced pain),
- reviewing lay research summaries to be included on webpages,
- providing input on webpage content,
- helping to brainstorm research design, intended outcomes and inclusion and exclusion criteria,
- conference organising committee membership (Advanced Pain Discovery Platform 2024 Conference)

PPAG is a vibrant group whose members are highly valued for their contributions. We routinely follow NIHR guidance on financial payment and reimbursement for PPIE involvement. A newsletter keeps PPAG members informed of achievements and activities.

Case Studies Illustrating PPIE

Case studies are appended describing how PPIE has fundamentally contributed to two projects within Pain Centre, improving the quality of research and its outcomes:

1. **Questionnaire to Assess Central Nervous System Aspects of Pain** (Dr Stephanie Smith, Stevie Vanhegan, Professor David Walsh).

   People with lived experience of arthritis pain have worked with Centre researchers to develop a questionnaire that measures central nervous system (brain/spinal cord) contributions to arthritis pain. The questionnaire is now a key tool in research across the world, has been translated into multiple languages, and is becoming a basis of personalized care for people with arthritis pain. Please see Appendix 1.

2. **The Pain-at-Work Toolkit** (Professor Holly Blake).

   People with lived experience of chronic pain have worked with Prof Blake and her team to develop and evaluate a toolkit that is designed to help working people, from diverse employment settings, to self-manage their pain at work. The aim is to help people to access support, enjoy a better work experience, and remain in the workforce. Please see Appendix 2.

Research Themes

Pain Centre research spans 5 major themes: (1) Biomarkers and Novel Therapeutic Targets, (2) Nociplasticity, (3) Neurocognitive and Psychological Function. (4) Treatment Efficacy and Real-World Evidence, and (5) Phenotyping and Personalised Medicine.

Below we summarise some of the advances that were made by the Pain Centre members in each theme, illustrating the diverse range of expert techniques and resources that were employed this past year.

Biomarkers and Novel Therapeutic Targets

Pain Centre Versus Arthritis is proud of its pioneering discoveries in biological targets research. It remains our ambition to shed light on previously unexplored molecular and cellular pathways which give rise to painful conditions. We have brought together evidence of key biomarkers for pain in osteoarthritis and after knee injury (O'Sullivan, et al., 2023a,b&c) to inform therapeutic target development. Our programme of

multiomics research is identifying often unexpected potential targets for novel analgesic development (Mehta et al., 2023, Vijay et al., 2023, Wei et al., 2023). We have furthermore explored potential biomarkers of adverse effects of opioids on brain structure, particularly when administered in early life (Taylor et al., 2023).

We continue to explore detailed cellular and molecular mechanisms of pain both in the joint (Wijesinghe et al., 2024), and in the central nervous system. An exciting area of novel research centres around extracellular vesicles (Anderson et al. 2023) and their capacity to mediate cell-cell communication. Extracellular vesicles have a tightly regulated cargo, including RNAs and may contribute to the detection of intracellular molecules in biofluids, and are functionally important in diverse biological process and organs, including allergy (Tucis et al., 2023) and pain (White et al., 2024).

We have continued intensive investigations of endogenous analgesic pathways. We have modelled pro-resolving 17-HDHA lipid pathways involved in OA pain (Franks et al., 2024) and confirmed the relevance of circulating biolipids as biomarkers of OA and post-injury joint pain (Turnbull et al., 2024a&b). Our work on opioid receptors and their ligands has further elucidated components of this complex endogenous analgesic system, helping to develop a pipeline for novel analgesic development that may retain analgesic efficacy whilst reducing risk (Bonifazi et al., 2023, Hill et al., 2023, Kirchhofer et al., 2023, Tsai et al., 2023, 2024, Underwood et al, 2024). We have developed oral and parenteral cannabidiol formulations and determined distribution across key brain regions relevant to pain relief (Brookes et al., 2023, Muresan et al., 2023).

Nociplasticity

`Nociplastic' refers to pain that is not adequately explained by tissue damage nor nerve pathology. Nociplastic pain results from altered responsiveness within the peripheral or central nervous system. Quantitative Sensory Testing (QST) is commonly used to measure pain hypersensitivity in humans, but can suffer from low repeatability due to influences from multiple factors. We have shown that reliability varies between different QST modalities, but not between people with low back or rheumatoid arthritis pain (Brady et al., 2023).

We have developed a simple questionnaire measuring Central Aspects of Pain (CAP) which associate with QST evidence of nociplasticity in people with knee pain. We have now validated the CAP questionnaire in people with rheumatoid arthritis, fibromyalgia (McWilliams et al., 2024), or low back pain (Georgopoulos et al 2024), as well as people with knee

osteoarthritis. Questionnaire scores suggest a common factor linking diverse aspects of central nervous system function across painful musculoskeletal conditions. Central Aspects of Pain scores were associated muscle strength (McWilliams et al., 2024) and with the ability of people with low back pain to self-manage their condition (Georgeopoulos et al., 2023).

Neurocognitive and Psychological Function

Neuroimaging provides evidence of the biological bases for neurocognitive and psychological morbidity in people with chronic pain. Medio-dorsal thalamic dysconnectivity in chronic knee pain provides a possible mechanism linking knee pain with negative affect (Iwabuchi et al., 2023).

We have developed fMRI methods to investigate brain connectivity in experimental rats (Grandjean et al., 2023), and also shown that central pain processing is modulated by chronic opioid use (Gonçalves et al, 2024). Our studies in rats have demonstrated key contributions increased pain sensitivity from NMDA receptors and astrocytes in the spinal cord, and important differences in pain biology between females and males.

Our increased understanding of brain connectivity has led us to develop novel approaches of transcranial magnetic stimulation (Briley et al., 2024, Drabek et al., 2023) which we anticipate will ultimately lead to new and effective non-pharmacological approaches to pain management. Brain connectivity may change following transcranial magnetic stimulation, explaining clinical improvement in depressive disorders (Briley et al., 2024). Moreover, transcranial magnetic stimulation of the motor cortex reduced nociplastic pain sensitivity (Hodkinson et al., 2024).

Our research into associations between pain and sleep disturbance has led us to propose that melatonin, already used for sleep disturbance, may provide effective pain relief for people with OA, with data from human and animal studies (Li et al., 2024). While much of our research seeks to explore pain mechanisms in individuals, we have also been able to show important cultural and country-level effects, emphasising the nature of pain as biopsychosocial problem (James et al., 2023).

Treatment Efficacy and Real-World evidence

We investigate treatment efficacy through systematic review and meta-analysis, and randomised controlled trials. We have shown how diverse pain measures may be harmonised as outcomes where data or biosamples are brought together from multiple feeder studies (Georgeopoulos et al., 2023). Our findings support the use of digital interventions to support pain self management in the workplace (Blake et al., 2024a), and to use rapid-

rather than modified-release opioids for acute post-surgical pain (Liu et al., 2023). We use systematic review and meta-analysis where single trials lack power to answer important questions, such as whether all placebos are equal (Balsby et al., 2024) and what predicts placebo response to intra-articular injection (Yu et al., 2024). We showed that exercise is similarly effective to paracetamol or non-steroidal anti-inflammatory drugs in osteoarthritis (Weng et al., 2023), and that analgesic medications may facilitate response to physiotherapy (Sveaas et al., 2023). Our expertise in evidence synthesis contributed to EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis (Moseng et al., 2024), and the 2023 ACR/EULAR classification criteria for calcium pyrophosphate deposition disease (Abhishek et al., 2023), and hand osteoarthritis (Haugen et al., 2024).

We have reported results of a feasibility randomised controlled trials testing a nurse-led package of care (Fuller, et al., 2024), combined exercise and weight reduction (Khazaei et al., 2024) or intra-articular ozone injection (Nazerieh et al., 2024) for knee pain, cognitive functional therapy for low back pain (Newton et al., 2024), and spinal medial branch nerve root block for vertebral fracture (Tan, 2023). We contributed to a multicentre randomised controlled trial showing that methotrexate could reduce OA pain (Kingsbury et al., 2024). We are currently undertaking a cluster randomised trial in workplaces across England, testing our Web-Based Pain-at-Work toolkit for employees with chronic or persistent pain (Blake et al., 2024b), and a mechanistic trial to explore the potential of response to intra-articular lignocaine injection to predict benefit from joint replacement surgery (Zedan, et al., 2023).

Unfortunately, benefits from treatment shown in randomised controlled trials do not always replicate in the real world. The real-world context often differs from the controlled environment of a trial. Our epidemiological studies have helped measure the high prevalence and impact of knee osteoarthritis and back pain (Weng et al., 2024, Coates et al., 2023, Swain et al., 2023), and analgesic use (Taqi et al., 2023). They have revealed potentially important factors that might exacerbate chronic pain, and consequences of it, including comorbidities and frailty (Chaplin et al., 2023, 2024), and depression (Ogliari et al., 2023). We have identified predictors and mapped changes over the years in opioid prescriptions after surgery, informing appropriate discontinuation of opioids when surgical pain has subsided (Baamer et al., 2023a&b, Pearcey et al., 2023). We explored possible sequelae of telehealth during the Covid pandemic on analgesic prescription (Vowles et al., 2024).

Our statistical analyses are complemented by qualitative research capturing the personal experiences of pain and its treatment in the real world, from perspectives both of patients (Kanavaki et al., 2023), and clinicians (Panchal et al., 2023). Detailed interviews showed how people with lived experience of pain often had a very different understanding of

what pain means compared to that which is supported by current research evidence (Walsh et al., 2023).

Phenotyping and Personalised medicine

A personalised medicine approach is at the heart of Pain Centre research. Our research helps direct patients away from the treatment strategies that for them do not work and encourages healthcare providers to customise therapies based on the patient's unique genetic makeup and disease phenotype.

Every individual is different, and average findings from groups of people often conceal substantial inter-individual variability. Chronic musculoskeletal pain can be a particular burden for people with other comorbidities. In people living with dementia there are challenges to recognising and diagnosing, never mind managing pain, all important factors for personalising treatment (Collins et al., 2023 & 2024). Pain impacts on personalised treatment for rheumatoid arthritis (McWilliams et al., 2023). Furthermore, people with osteoarthritis may be at high risk of developing comorbidities (Kamps et al., 2023a&b). Explanations for these associations may be complex, involving genetic risk factors, lifestyle adaptations and medication use. A novel area that our research is highlighting relates to the gut microbiome, in which individual signatures may be associated with anxiety and depressive symptoms (Kouraki et al., 2023). Our research that pain itself is not a single thing, and our work on pain phenotyping has given novel insights into the ways in which people with arthritis pain might most meaningfully be allocated to specific subgroups who might respond differently to different treatments (Smith et al., 2024).

Organisational Structure

Co-directors

Name	School and Faculty	Position	Area of Expertise
Prof Victoria Chapman, Pain Centre Executive Committee Member	School of Life Science; Faculty of Medicine and Health Sciences	Co-Director of Pain Centre Versus Arthritis; Professor of Neuropharmacology	In vivo studies, pharmacological intervention, pain biomarkers, CNS function, forward and back translation.

Prof David Andrew Walsh, Pain Centre Executive Committee Member	School of Medicine; Faculty of Medicine and Health Sciences	Co-Director of Pain Centre Versus Arthritis; Professor of Rheumatology and Consultant Rheumatologist at Sherwood Forest Hospitals NHS Foundation Trust.	Pain phenotyping in arthritis, mechanistic pain modelling and assessment across preclinical and clinical studies, pharmacological and non-pharmacological therapeutic intervention, biorepositories.

Executive Committee

Name	School and Faculty	Position	Area of Expertise
Dr Duncan Hodkinson	School of Medicine; Division of Mental Health and Clinical Neuroscience	Senior Research Fellow	Imaging; pain & neuroscience
Prof Eamonn Ferguson	School of Psychology; Faulty of Science	Professor of Health Psychology	Health psychology, cohort studies, statistical modelling, psychosocial impact
Dr Federico Dajas-Bailador	School of Life Sciences Faculty of Medicine and Health Sciences	Associate Professor	Physiology Pharmacology and Neuroscience, regulation of axonal protein expression by selective degradation
Dr Roger Knaggs	School of Pharmacy; Faculty of Science	Associate Professor	The appropriate use of analgesic medicines, and associated clinical outcomes and healthcare utilisation
Prof Weiya Zhang	School of Medicine; Faculty of Medicine & Health Sciences	Professor of Epidemiology	Epidemiology, evidence-based medicine, osteoarthritis, Gout Research, comorbidities and multimorbidity

Senior Investigators

Name	School and Faculty	Position	Area of Expertise
Prof Abhishek Abhishek	School of Medicine; Faculty of Medicine and Health Sciences	Professor of Rheumatology Honorary Consultant Rheumatologist, Nottingham University Hospitals NHS Foundation Trust	Autoimmune Rheumatic Disease Epidemiology, Gout, CPPD, OA clinical research, Clinical Trials - CTIMPs, Pragmatic trials, Ultrasound imaging
Prof Ana Valdes	School of Medicine Faculty of Medicine and Health Sciences	Professor of Molecular and Genetic Epidemiology	Metabolomics, Gut microbiome, metabolic syndrome, nutrition, inflammation, osteoarthritis
Dr Anna Piccinini	Faculty of Science	Assistant Professor	Inflammation Biology
Prof Avril Drummond	School of Heath Sciences; Faculty of Medicine and Health Sciences	Professor of Healthcare Research	Healthcare research and occupational therapy, stroke rehabilitation and rehabilitation research
Prof Benjamin Ollivere	School of Medicine; Faculty of Medicine and Health Sciences	Professor of Orthopaedic Trauma Surgery, Honorary Consultant Orthopaedic Trauma Surgeon and Major Trauma Surgeon at Queens Medical Centre. Head of Department for Trauma, Orthopaedics and Sports Medicine.	Non-union, bone infection, trauma and major injury along with treatment of complex fractures and the complications of these treatments; interest in limb reconstruction

Dr Benjamin Smith	Faculty of Medicine & Health Sciences	Honorary Assistant Professor, School of Medicine	Clinical research physiotherapist
Prof Brigitte Scammell	School of Medicine; Faculty of Medicine and Health Sciences	Consultant Orthopaedic Surgeon in adult foot and ankle surgery, Emeritus Professor	Orthopaedic surgery, biology of fracture healing, osteoarthritis and biomaterials
Dr Cornelia De Moor	School of Pharmacy; Faculty of Science	Associate Professor in RNA Biology	Messenger RNA, protein synthesis, gene expression, polyadenylation, cordyceptin, Cordyceps
Dr Daniel McWilliams	Faculty of Medicine & Health Sciences	Senior Research Fellow	Pain researcher, specialising in pain mechanisms in musculoskeletal conditions
Dr Daniel Scott	Faculty of Medicine & Health Sciences	Research Fellow	Induced pluripotent stem cell (iPSC) models to understand and target rare human diseases including motor neurone diseases.
Dr Dong-Hyun Kim	School of Pharmacy; Faculty of Science	Associate Professor	Analytical Bioscience
Prof Dorothee Auer	School of Medicine; Faculty of Medicine and Health Sciences	Professor of Neuroimaging	Clinical neurosciences using advanced MRI techniques
Dr Fiona Moffatt	School of Heath Sciences; Faculty of Medicine and Health Sciences	Associate Professor	Qualitative methodologies, Ethnography, Implementation Science, First Contact Physiotherapy, Swimming and equative exercise to promote health

Dr Galina Pavlovskaya	School of Medicine; Faculty of Medicine and Health Sciences	Associate Professor, Translational Imaging	Translational and Molecular Imaging
Dr Gareth Hathway	School of Life Sciences; Faculty of Medicine and Health Sciences	Associate Professor, Director of Neuroscience	Science of pain and nociception, pain processing
Prof Holly Blake	School of Health Sciences; Faculty of Medicine and Health Sciences	Professor of Behavioural Medicine	Health promotion and behaviour change; self-management of chronic conditions; behavioural interventions to promote self-care practices and health behaviours; work and health.
Dr Isabella Maiellaro	School of Life Sciences; Faculty of Medicine & Health Sciences	Ann Mclaren Fellow	GPCR-mediated synapticplasticity
Dr Jemima Collins	Faculty of Medicine & Health Sciences	Clinical Associate Professor in Health Care of Older People	Health Care of Older People; clinical research in ageing populations with chronic pain
Dr Joanne Stocks	School of Health Sciences; Faculty of Medicine and Health Sciences	Assistant Professor in Rehabilitation Technology	Healthy aging, focusing on the role of biomarkers, nutrition, gut microbiome, osteoarthritis and pain
Prof Joe Kai	School of Medicine; Faculty of Medicine and Health Sciences	Clinical Professor	Expertise in clinical and applied health research,teaching and service development
Prof John Gladman	School of Medicine	Emeritus Professor of Medicine of Older	Expertise in pain and

		People	frailty/dementia
Prof Kate White	Faculty of Medicine & Health Sciences	Deputy Head of School, Clinical Director of SVMS, Head of Division of Veterinary Clinical Sciences	Veterinary Medicine and Science
Dr Kim Chisholm	School of Life Sciences; Faculty of Medicine & Health Sciences	Ann Mclaren Research Fellow	In vivo microscopy to elucidate nervous system function and dysfunction; neural networks underpinning pain and sensation.
Dr Louise Wilson	Faculty of Science	Assistant Professor	Opioid prescribing and the role of Community Pharmacy; Pain management in Community Pharmacy
Prof Marilyn James	School of Medicine; Faculty of Medicine and Health Sciences	Professor of Health Economics	Health Economist and expert in economic evaluation
Prof Meritxell Canals Buj	School of Life Sciences; Faculty of Medicine and Health Sciences	Professor of Cellular Pharmacology	Interactions between G Protein-Coupled Receptors and intracellular proteins, and their consequences for receptor signalling and trafficking
Professor Michael Doherty	Faculty of Medicine and Health Sciences	Emeritus Professor of Rheumatology	Osteoarthritis, gout, calcium pyrophosphate crystal deposition (CPPD), placebo/contextual response and evidence-based medicine.

Prof Michael Stocks	School of Pharmacy; Faculty of Science	Professor of Medicinal Chemistry and Drug Discovery. Associate Professor, Centre for Biomolecular Sciences	Drug Discovery, Design, Medicinal and Synthetic Chemistry
Dr Michelle Hall	School of Health Sciences; Faculty of Medicine and Health Sciences	Assistant Professor Physiotherapy and osteoarthritis	Musculoskeletal rehabilitation and rheumatology
Prof Paul Greenhaff	School of Life Sciences; Faculty of Medicine and Health Sciences	Professor of Muscle Metabolism	Skeletal muscle metabolism, growth and atrophy; nutritional, physiological and pharmacological strategies to alter skeletal muscle metabolism and function, skeletal muscle fatigue
Dr Paul Hendrick	School of Health Sciences; Faculty of Medicine and Health Sciences	Assistant Professor in Physiotherapy and Rehabilitation Sciences	Low back pain research, Pain Research focused on the role of exercise and physical activity, pedagogy of Clinical Reasoning
Dr Pavel Gershkovich	School of Pharmacy; Faculty of Science	Associate Professor of Biopharmaceutics	Biopharmaceutics, Pharmacokinetics, Pharmacodynamics, Bioanalytical Techniques, Oral Drug Delivery, Effects of Disease States on Pharmacokinetics and Pharmacodynamics
Prof Penny Gowland	School of Physics & Astronomy; Faculty of Sciences	Professor of Physics	Developing quantitative MRI for biomedical applications
Dr Richard James	Faculty of Science	Assistant Professor	Addictive behaviours

Dr Richard Pearson	School of Medicine; Faculty of Medicine and Health Sciences	Assistant Professor	Quantified changes in bone associated with several disease pathologies
Dr Rob Lane	School of Life Sciences; Faculty of Medicine and Health Sciences	Associate Professor of Molecular Pharmacology	G protein-coupled receptors with a particular emphasis on novel approaches towards the development of improved therapeutics for CNS disorders
Prof Roshan das Nair	School of Medicine; Faculty of Medicine & Health Sciences	Professor of Clinical Psychology and Neuropsychology	Multiple sclerosis, Acquired brain injury, Pain research
Dr Stefan Kluzek	School of Medicine; Faculty of Medicine & Health Sciences	Clinical Associate Professor	Sports and Exercise Medicine
Dr Stephen Ryder	Faculty of Medicine & Health Sciences	Consultant Physician	Hepatology and Gastroenterology
Dr Stephanie Smith	Faculty of Medicine & Health Sciences	Senior Research Fellow	Pain management in rheumatic and musculoskeletal diseases.
Mr Thomas Kurien	School of Medicine; Faculty of Medicine & Health Sciences	Clinical Associate Professor	Clinical Associate Professor of Knee Surgery and Honorary Consultant Knee Surgeon
Dr Tobias Bast	School of Psychology; Faculty of Science	Associate Professor	Bain mechanisms of cognition and behaviour; neuroscience and biological psychology

Dr Vasileios Georgopoulos	Faculty of Medicine & Health Sciences	Research Fellow	Pain self-management, pain management, low back pain, Musculoskeletal Health, Quantitative Sensory Testing
Dr Victoria James	Faculty of Medicine & Health Sciences	Associate Professor	Cancer Biology and GeneExpression

Research Fellows and Early Career Researchers

Name	School and Faculty	Position
Dr Fuller, Amy	Faculty of Medicine & Health Sciences	Research Fellow
Dr Nakafero, Georgina	Faculty of Medicine & Health Sciences	Research Fellow
Dr Chitra Joseph	Faculty of Medicine & Health Sciences	Research Fellow
Dr Clive Jabangwe	Faculty of Medicine & Health Sciences	Research Associate
Dr Giulia Ogliari	Faculty of Medicine & Health Sciences	Associate
Dr Hannah Jackson	Faculty of Medicine & Health Sciences	Research Fellow
Dr James Turnbull	Faculty of Medicine & Health Sciences	Research Fellow
Dr Jyoti Agrawal	Faculty of Medicine & Health Sciences	Research Fellow
Dr Li Li	Faculty of Medicine & Health Sciences	Senior Research Fellow
Dr Onosi Ifesemen	Faculty of Medicine & Health Sciences	Research Fellow
Dr Stephen Woodhams	Faculty of Medicine & Health Sciences	Research Fellow
Dr Tameille Valentine	Faculty of Medicine & Health Sciences	Research Fellow
Wendy Chaplin	Faculty of Medicine & Health Sciences	Research Associate
Dr Will Thompson	Faculty of Medicine & Health Sciences	Research Fellow

Research Support

Name	School and Faculty	Position
Deborah Wilson	Sherwood Forest Hospitals NHS Foundation Trust	Research Nurse
Doris Chu	Faculty of Medicine & Health Sciences	Administrative Co-ordinator
Dr Laura Wyatt	Faculty of Medicine & Health Sciences	Clinical Trial Manager
Liz Dennis	Faculty of Medicine & Health Sciences	Senior Administrator
Paul Millns	Faculty of Medicine & Health Sciences	Senior Technical Specialist
Sean McLoughlin	Faculty of Medicine & Health Sciences	Musculoskeletal Research Administrator
Dr Seyed Shahtaheri	Faculty of Medicine & Health Sciences	Histology Technician
Tom Gray	Faculty of Medicine & Health Sciences	Musculoskeletal Research Administrator
Dr Tony Kelly	Faculty of Medicine & Health Sciences	Research Fellow

Students

Name	Project Title	Start Date	Supervisors
Ahmed Thanoon	Prevalence and associated risk factors of foot/ankle osteoarthritis and neurodegenerative conditions in ex-professional footballers compared to general population	October 2021	Professor Weiya Zhang (Principal Supervisor) Professor Michael Doherty (co-supervisor) Dr Shima Espahbod (co-supervisor)
Angela Higgins	Co-Design of Assistive Robotic Systems for Monitoring and Management of Chronic Pain	October 2022	Professor Praminda Caleb-Solly, Professor Holly Blake, Dr Michelle Hall
Aya Abd Elkhabir	Personalised approaches to the management of chronic musculoskeletal	October 2021	Prof. David Walsh (Principal Supervisor), and Dr Daniel McWilliams

	pain in people with Rheumatoid Arthritis		
Ayah Ismail	Optimising contextual effects in the patient-practitioner interaction in the management of osteoarthrtitis	October 2018-2023	Prof Weiya Zhang, Prof Michael Doherty
Charles Besidonne	Alternative splicing targets inarthritis	October 2021	Jeanette Woolard, Andrew Benest, Kim Chisholm, David Bates
Dalin Shaban	The Use of Digital Messaging Intervention to Promote Physical Activity in Patients with Knee Osteoarthritis in Saudi Arabia: A feasibility Study.	October 2023	Dr Paul Hendrick, Professor Holly Blake
Fahad Alotibi	Virtual Reality for Chronic Low Back Pain: A Mixed Methods Feasibility Study in the Kingdom of Saudi Arabia	October 2021	Paul Hendrick, Fiona Moffatt
Hayley Carter	The Pre-Operative Management of Patients Awaiting Anterior Cruciate Ligament Reconstruction (The POP-ACLR Study)	March 2022	Professor Pip Logan, Dr Fiona Moffatt, Dr Laul Leighton, Dr Benjamin Smith
Lauren Brown	Investigating opioid tolerance at the cellular level and its relationship with its behavioural Manifestations	October 2021	Prof MeritxellCanals Buj
Maria Alshammari	Chronic Pain Management for	April 2023	Paul Hendrick

	Children and Adolescents in Saudi Arabia		
Monira Parveen	The role of TLR2 signalling in sensory neurons and long term pain response	December 2023	Professor Victoria Chapman, Professor Gareth Hathway
Monirah Shuaib	Osteoarthritis and multimorbidity in male retired professional footballers compared to men in the general population controls	February 2021	Prof. Weiya Zhang,Prof. Michael Doherty, Dr Michelle Hall and Dr Subhashisa Swain
Neave Smith	Early life exposure to opioids and pain in later life	May 2023	Gareth Hathway, Victoria Chapman
Nouf Al-Otaibi	Epidemiology of Chronic shoulder pain and associated risk factors in the United Kingdom: a population-based study of UK primary care data using clinical practice research datalink (CPRD)	April 2021	Michelle Hall, Weiya Zhang, Subhashisa Swain,Michael Doherty, Yana Vinogradova
Prajakta Bhoir	Age related changes in serotonergic pathways and pain processing	September 2022	Gareth Hathway, Victoria Chapman
Rebecca Pope	The effect of inflammatory signalling on DRG sensory neuronal excitability	September 2021	Dr Federico Dajas-Bailador, Gareth Hathway
Reham Baamer	Postoperative pain assessment and opioid utilisation following colectomy	October 2019	Dr Roger Knaggs,Li Shean Toh, Dileep Lobo
Roheena Sohail	Arthritis damage and pain: VEGF	October 2018-2024	Prof Lucy Donaldson

	involvement		
Sophie McCann	Role of cancer cell derived extracellular vesicles in neuron development and connectivity	September 2023	Federico Dajas- Bailador, Gareth Hathway, Beth Coyle
Walid Mohamed	Arabic translation, cultural adaptation, and psychometric validation of a measure of patient's outcome expectations in the musculoskeletal population	April 2022	Paul Hendrick
Yasmine Zedan	Understanding pain mechanisms in knee osteoarthritis	October 2018	Dorothee Auer, Professor Brigitte Scammell, Mr TomKurien

Active Funding, Awards and Grants

Senior Investigator(s)	Awarded By	Details	Period
Abhishek Abhishek (CI), Weiya Zhang (co-I)	NIHR HTA	Treat to target for gout (T2T)	2018-2025
Ana Valdes	Versus Arthritis	Synovial fluid to define endotypes by unbiased proteomics in OA	2010-2024
Ana Valdes, Andreas Goebel, Afroditi Kouraki, Thomas Kurien, Benjamin Smith	Versus Arthritis	Identifying molecular mechanisms underlying pain relief response to physiotherapy in people with osteoarthritis	2023-2026
Ana Valdes, Stefan Kluzek, Benjamin Smith	UK Research and Innovation	Molecular signatures of endocannabinoid induced pain relief in humans: lifestyle interventions, systemic and localised changes.	2022-2025

Benjamin Ollivere	National Institute for Health Research	Erector Spinae Plane blocks for the Early Analgesia of Rib fractures in trauma: a feasibility randomised controlled trial with embedded qualitative assessment (ESPEAR trial).	2021-2024
Benjamin Ollivere	Smith and Nephew	smart TSF Software analysis	2021-2023
Benjamin Ollivere	AO Foundation	Muscle Phenotyping in frail older patients having hip surgery following fracture	2021-2023
Benjamin Ollivere	National Institute for Health Research (NIHR) Evaluation Trials and Studies	The ORiF (Operative Rib Fixation) Procedure mEchanisms of Rib fixAtion (OPERA) STUDY Coordinating Centre	2021-2023
David Walsh	UK Research and Innovation /Versus Arthritis	Advanced Pain Discovery Platform (APDP) – Programme Director	2023-2025
DA Walsh (CI). Co-applicants: D Auer, V Chapman, M Doherty, E Ferguson, S Kelly, B Scammell, K Vedhara, W Zhang.	Versus Arthritis	Centre Initiative Grant: Pain Centre Versus Arthritis	2015-2027
David Walsh	Versus Arthritis	Improving pain outcomes in rheumatoid arthritis; detecting the contribution of central pain mechanisms.	2020-2023

David Walsh	National Institute for Health Research	Biomedical Research Centre (musculoskeletal theme NIHR/NOCRI Musculoskeletal-Translational Research Collaboration for MSK, Trauma, Surgery and Recovery theme)	2022-2027
David Walsh	GlaxoSmithKline Research and Development Ltd	Analysis of paired synovium and DRG samples from OA donors	2023-2025
David Walsh	Orion Corporation	Evaluation studies of the expression of pain targets on osteoarthritis tissues and the association of target expression withosteoarthritis pain.	2022-2024
David Walsh, Victoria Chapman	Eli Lilly & Co	Human validation for novel targets associated with OA pain	2020-2024
Dorothee Auer	Wellcome Trust	Midlands Mental Health & Neurosciences PhD Programme for Healthcare Professionals	2022-2029
Dorothee Auer	Engineering and Physical Sciences Research Council	Realising the potential of open MRI for dynamic studies of human anatomy and function	2021-2024
Federico Dajas-Bailador, Victoria Chapman	Eli Lilly and Company (USA)	Role of novel molecular candidates in pain	2024-2026

Gareth Hathway, Dr Lianne Wood, Professor Sallie Lamb	NIHR Programme Development Grant	Development of a prehabilitation intervention for people with spinal stenosis undergoing spinal surgery	2023
Gareth Hathway (PI), Dajas-Bailador (CO-I), Beth Coyle (Co-I), Anna Grabowaska (Co-I), Vicky James (Co-I)	Medical Research Foundation	Extracellular vesicles as conduits for the transfer of biologically active compounds which mediate cancer chemotherapy based pain in early life	2023-2026
Holly Blake, David Walsh, Daniel McWilliams	Nuffield Foundation and Versus Arthritis	The PAW Trial - Randomised Controlled Feasibility Trial to Assess Potential Effectiveness and Cost Effectiveness of the Pain at Work Toolkit in Employees with Chronic or Persistent Pain	2023-2025
Isabella Maiellaro, Federico Dajas-Bailador	BBSRC	PaRTIS: Peripheral RNA translation in sensitization	2024-2027
Jemima Collins (PI); David Walsh (Co-I)	NIHR	CAPPPeD (Central Aspects of Pain in People living with Dementia)	2023-2025
Jemima Collins	Nottingham Hospitals Charity	Hospital Experiences of Pain in People living with Dementia	2024-2025
Joanne Stocks	Research England	Investigating Microbiome Diversity in the UK Population - Public Engagement	2023-2023

Kim Chisholm	BBSRC	A brighter future cutting-edge multiphoton imaging at Nottingham	2023-2024
Kim I Chisholm	University of Nottingham	Illuminating the spinal cord to understand chronic pain: In vivo imaging of somatosensory responses of spinal networks	2022-2025
Kim I Chisholm	Royal Society	Shedding light on chronic cold pain: The role of spinal cord networks in cold hypersensitivity	2022-2023
Michelle Hall, Paul Hedrick	NRC Research Fund	Developing a core outcome set for complex fractures	2023-2024
Roger Knaggs	NIHR Applied Research Collaborative	A descriptive study of antidepressant use in people prescribed opioids for non-cancer pain.	2022-2023
Roshan das Nair	National Institute for Health Research (NIHR) Programme Grants for Applied Research	Multicentre Research Programme to Enhance Return to Work after Trauma (ROWTATE)	2019-2024
Simon Jones (PI), Vicky Chapman (Main Co-I), F. Dajas-Bailador (Main Co-I), Edward Davis (Co-I), Georgios Gkoutos (Co-I), Mark Lindsay (Co-I).	MRC APDP Platform Grant	MICA-Synovial fibrobasts pain phenotypes: a roadmap to understanding and targeting the complexity of patient reported joint pain in osteoarthritis.	2022-2025

Stefan Kluzek	Versus Arthritis	Biomarkers and Joint Pain in Military Osteoarthritis Study (Bio-Mil-OA)	2020-2023
Stephanie Smith, David Walsh, Mathew Piasecki, Fiona Moffatt	NIHR Nottingham BRC/SoM	Pain increases disability; disability increases pain PhD Studentship	2024-2027
Stephanie Smith, David Walsh, Fiona Moffatt	EULAR	Qualitative evaluation of a tool to optimise the diagnosis and measurement of a predominant contribution of the central nervous system to chronic RMD pain	2023-2024
Stephanie Smith, Caroline Abbott, Kirsty Bannister, David Walsh, Stevie Vanhegan	Versus Arthritis	Assessing central nervous system contributions to accelerate musculoskeletal pain diagnosis and treatment	2023-2026
Vasileios Georgopoulos Holly Blake, Daniel McWilliams, David Walsh, Fiona Moffatt	The Thalidomide Trust	Thalidomide-Related Investigation on Understanding and Managing Pain in Thalidomide Survivors	2024
Victoria Chapman (PI) and F. Dajas-Bailador (Co-PI), Ana Valdes (Co-I), Don-Hyun Kim (Co-I), David Bennett (Co-I), Andreas Themistocleous (Co-I), Peter Gowler (RCo-I).	MRC APDP Platform Grant	MICA-Exploring specialised pro-resolution molecule mediated analgesia to identify novel targets for the treatment of chronic pain.	2022-2025

Victoria Chapman (PI), Ana Valdes (Co-I), Daniel Scott (Co-I), David Walsh (Co-I), Dong-Hyun Kim (Co-I), Federico Dajas-Bailador (Co-I), Ian Kerr (Co-I), James Turnbull (RCo-I), Stephen Alexander (Co-I), Thomas Kurien (Co-I), Vasileos Georgopoulos (R&IA)	Medical Research Council	Targeting the therapeutic potential of soluble epoxide hydrolase for the treatment of osteoarthritis pain.	2025-2028
Victoria Chapman, Gareth Hathway, Steve Woodhams	Medical Research Council	Mechanistic studies of opioid-induced exacerbation of chronic pain responses	2022-2025
Victoria Chapman	Versus Arthritis	Harnessing the potential of 17-HDHA a novel biomarker of OA pain status	2019-2024
F Boissonade (PI, Sheffield), Victoria Chapman, David Walsh	Versus Arthritis	Lymphotactin in arthritis pain	2020-2024
Victoria Chapman and Dong-Hyun Kim	University of Nottingham	Nano-electrospray ionisation source for nano-liquid chromatography system to establish new methods for the detection of low abundance endogenous opioid peptides in biological samples	2023-2024

Weiya Zhang (CI) Carol Coupland (Co-I) Michael Doherty (Co-I)	FOREUM	Comorbidity in osteoarthritis (comOA)	2019-2024
Weiya Zhang (CI) Michael Doherty (Co-I)	FOCUS	Foot/ankle OA and Cognitive Impairment in the UK Soccer players (FOCUS)	2019-2024
Weiya Zhang (PI) Michelle Hall (Co-I)	NIHR SPR	Optimising the Provision of Therapeutic Exercise for People with Knee and/or Hip Osteoarthritis in Primary Care: An Individual Participant Data Network Meta-analysis (the OPTEX study)	2024-2026

Our commitment to collaboration is reflected by a portfolio of current collaborative grants.

Senior Investigator(s) and Institution	Awarded By	Details	Period
Gordon Milligan and Chris Cole (Cis, Dundee). Co-Is. Ana Valdes and Weiya Zhang	UK Research and Innovation/ Versus Arthritis	Advanced Pain Platform ALLEVIATE Data Hub for Pain	2021-2024
Simon Jones, University of Birmingham (PI), Victoria Chapman, Federico Dajas-Bailador, University of Nottingham (Co-I),	UK Research and Innovation/ Versus Arthritis	APDP: Synovial fibroblast pain pathotypes: A roadmap to understanding and targeting the complexity of patient-reported joint pain in osteoarthritis	2022-2025

Mohammad Al-Amri, Cardiff University (PI), David Walsh, University of Nottingham (Co-I)	Versus Arthritis	A randomised feasibility study to evaluate home-based personalised virtual reality physiotherapy rehabilitation compared to usual care in the treatment of pain for people with knee osteoarthritis	2022-2025
Christian Mallen, Keele University (PI); Roger Knaggs (Co-I)	National Institute for Health Research (NIHR)	Improving outcomes for patients with opioid-treated persistent non-cancer pain: a proactive clinical pharmacist-led primary care intervention (PROMPPT intervention).ACRONYM: Pharmacist-led intervention to Reduce inappropriate use of Opioid Medicines and optimise Persistent Pain Therapy (PROMPPT)	2019-2025
Andrew Price, University of Oxford (PI); Stefan Kluzek (Co-I); Anna Valdes (Co-I).	National Institute for Health Research (NIHR)	Genicular Artery Embolisation for the symptomatic treatment of knee osteoarthritis refractory to conservative management (GEKO)	2023-2026
Rachel Gooberman-Hill, University of Bristol (PI), David Walsh (PI)	National Institute for Health Research (NIHR) Programme Development Grant (PDG), NIHR202618	Support and treatment after joint replacement (STAR): translation into practice and long-term follow up	2021-2023

Publications 2023 – 2024

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Appendices

Appendix 1: Patient and Public Involvement Case Study 1:

A questionnaire to assess central nervous system aspects of pain

Stephanie Smith (academic), Stevie Vanhegan (PPAG member) and David Walsh (academic), on behalf of Pain Centre Versus Arthritis

What people feel as pain is not simply a question of what is happening in their joints. The brain and spinal cord (central nervous system) decides how we feel pain. Sometimes, it can make pain feel worse, and sometimes it can reduce pain. How the central nervous system is involved in pain can be measured using special tests such as quantitative sensory testing (QST) and magnetic resonance imaging of the brain (MRI). In QST, heat, cold or mechanical pressure is applied to the individual who is asked to describe whether or how painful it is. Brain fMRI can make some people feel anxious or claustrophobic. These tests can be time-consuming, require specialist equipment, and are sometimes unpleasant. Pain Centre Versus Arthritis is a partnership between people with lived experience of pain and researchers with expertise in how the brain and spinal cord work. This partnership has enabled us **to develop a simple questionnaire to detect and measure these central nervous system aspects of pain: the Central Aspects of Pain (CAP) Questionnaire.**

People with lived experience of pain, the Centre's Patient and Public Advisory Group (PPAG), are essential to the work of Pain Centre Versus Arthritis. Their valuable insights contributed to the Centre's successful application to Versus Arthritis in 2015 to fund a 5-year programme of research exploring the mechanisms of arthritis pain and develop improved treatments. They contributed through focus groups, sharing and reviewing ideas and ensuring that what we put in writing was meaningful. Pivotal to that research, we established a (Knee Pain In the Community: KPIC) of approximately 9,500 people who completed annual 20-page questionnaires about their arthritis and pain over the 5 year period.

People from the KPIC cohort attended the University of Nottingham for a detailed assessment of their pain. Kehinde Akin-Akinyosoye, a PhD student within the Centre, worked with individuals with knee pain to refine the 20-page questionnaire booklet. They produced a simple 8-question questionnaire that contained only the best questions to detect and measure central aspects of pain. Kehinde interviewed 30 people experiencing knee pain to make sure that the questionnaire made sense to them. We then changed some questions in response to their difficulties

and comments. By doing this, we could ensure that people answered the questionnaire in a way that matched the scientific intentions behind each question. For example, we adapted the question about pain experienced in response to heat or cold to clarify that it meant contact with a hot or cold object or water, rather than the ambient temperature in the winter or summer.

The modifications resulted in the Central Aspects of Pain (CAP) questionnaire, a user-friendly and practical tool. It brings together many different aspects of the pain experience, such as anxiety, depression, catastrophizing, fatigue, sleep disturbance, and difficulty thinking straight. CAP is a simpler method to assess an individual's pain experience than tests such as QST or MRI. It has many other advantages. It opens the way in the NHS for more routine assessment of important brain and spinal cord contributions to arthritis pain.

Positive feedback from the Pain Centre's Patient and Public Advisory Group (PPAG) resulted in CAP's inclusion in the questionnaire booklet for a second large group of people with musculoskeletal pain (the Investigating Musculoskeletal Health and Wellbeing Survey: IMH&W). Some of these people had knee pain. Others had pain elsewhere. Inclusion in IMH&W enabled further refinement of the questionnaire so that people with pain at sites other than the knee could now use it. Through discussions with people with lived experience of pain, we now know that the CAP questionnaire validly measures central aspects of pain in people with low back pain, rheumatoid arthritis or fibromyalgia, as well as in people with osteoarthritis. A satisfaction survey showed that a large majority (92%) of people in one study found CAP easy to follow, and almost all (99%) would be happy to complete the questionnaire again. Very few (4%) questionnaires could not be scored because of questions having been left unanswered. This information tells us that CAP is easy to use and acceptable to people with arthritis pain.

We then looked at applying the CAP questionnaire to those with an even broader range of musculoskeletal conditions. People with rheumatoid arthritis contributed to a focus group, highlighting the importance of pain that does not get better despite the optimal use of anti-inflammatory treatments. Two members of this group contributed as co-applicants to successful funding applications to Versus Arthritis and Pfizer Ltd. Research studies often need to have a Steering Committee, to make sure that everything goes as planned, or to find ways to work around any difficulties that are encountered. The 2 study co-applicants with lived experience of arthritis were key members of the Central Aspects of Pain in Rheumatoid Arthritis (CAP-RA) Steering Committee. In the CAP-RA study,

we used the CAP questionnaire to understand interactions between inflammation and central nervous system mechanisms in people with painful rheumatoid arthritis. People with lived experience undertook a walk-through of the study visit (the study visit required people to come to the hospital and undertake several assessments of their pain). Together, we refined and streamlined these visits, thinking about the order in which we undertake assessments and what participants could complete more conveniently at home. The Steering Committee members with rheumatoid arthritis enabled us to think about recruitment from a patient perspective during the many COVID-19 spikes. The Steering Committee members and other members of the Pain Centre's PPAG have worked with researchers to prepare scientific reports and summaries that are accessible to patients and the public, explaining what we have found and the importance of the findings. The CAP questionnaire can now detect central aspects of pain in people with a wide range of musculoskeletal conditions.

We are currently exploring how the CAP questionnaire can identify people who could benefit from specific treatments in clinical practice and research trials. By better understanding the precise mechanisms underlying the central aspects of pain, we can develop new and better treatments to relieve the burden of arthritis pain. Specifically, people with lived experience of pain and researchers have co-produced two new and successful research funding applications building on our work with the CAP questionnaire:

1) The Assessing Central Nervous Systems Contributions to Accelerate Musculoskeletal Pain Diagnosis and Treatment (AsCent) project explores combining the CAP questionnaire with a simplified version of QST to help manage arthritis pain. Versus Arthritis and EULAR now fund this study.

2) An NIHR-funded project is investigating pain in people living with dementia (CAPPPeD) using CAP.

In each project, people with lived experience of pain contribute as equal partners as members of the study Steering Committees, providing valuable input and insight into the study's management and running. Together with people with lived experience of pain, we summarise all articles accepted for publication in scientific journals so that they can be understood by a non-specialist audience. Members of the Centre's PPAG (all of whom have lived experience of pain) review these summaries to ensure that they are understandable and adequately address concerns of people with lived experience of pain before being posted on the Centre's website at https://www.nottingham.ac.uk/paincentre/publications/lay-summaries.aspx .

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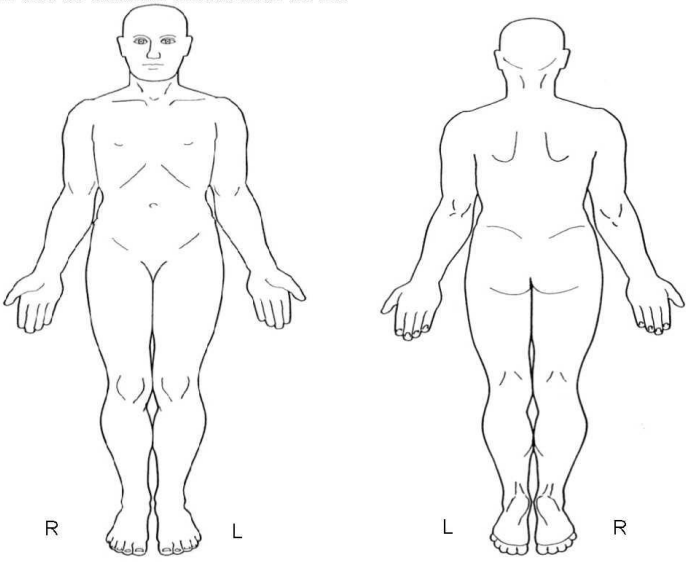
Central Aspects of Pain (CAP) Questionnaire

Please select the response that best describes how you have felt over the PAST *WEEK*. Joint pain may be due to pain in any of your joints, such as fingers, wrist, toes, knees, hips, etc. Please tick one box only r statement and try not to leave any statements blank.

		never	sometimes	often	always
1.	Cold or heat (e.g., bath water) on my joint was painful	☐	☐	☐	☐
2.	I generally felt tired	☐	☐	☐	☐
3.	My joint pain stopped me concentrating on what I was doing	☐	☐	☐	☐
4.	I kept thinking about how much my joint hurts	☐	☐	☐	☐
5.	In general, I got sudden feelings of panic	☐	☐	☐	☐
6.	Joint pain affected my sleep	☐	☐	☐	☐
7.	I generally still enjoyed the things I used to enjoy	☐	☐	☐	☐

8. This next question is about pain you may have had in any part of your body. Please shade in the diagram below, to indicate where you have suffered any pain for most days in the last ***4 WEEKS***. By pain we also mean aching and/or discomfort. Please do not include pain due to feverish illness such as flu.



McWilliams *et al.*, Validation of a questionnaire for central nervous system aspects of joint pain: the CAP questionnaire. *Rheumatology* 2024 doi: https://doi.org/10.1093/rheumatology/keae342

Appendix 2: Patient and Public Involvement Case Study 2

The Pain-at-Work Toolkit

Professor Holly Blake

Self-management tools for people with chronic or persistent pain tend to focus on symptom reporting, treatment programmes or exercise and do not address barriers to work, facilitators of work ability, or workplace pain self-management strategies. In response to this, we developed the Pain-at-Work (PAW) toolkit which provides (a) evidence-based guidelines and signposting around work-capacity advice and support; (b) self-management strategies around working with chronic or persistent pain, (c) promotion of healthy lifestyles, and quality of life at work; (d) advice on adjustments to working environments and workplace solutions to facilitate work participation.

The toolkit was co-created with input from 472 people including healthcare professionals, employers and people living with chronic or persistent pain. This included a stakeholder consultation event (n=27), an online survey with people who have chronic pain (n=274), an online employer survey (n=107) and an expert peer review panel which included people with lived experience (n=40). This process helped us to design the content, presentation and delivery approach for the toolkit, which we updated and refined through a group concept mapping exercise with input from our PPIE partner, Victoria Abbott-Fleming (Chair of the Patient Voices Committee, British Pain Society). Prior to testing the toolkit in a trial, we conducted a pilot test of the toolkit and evaluated it through an online survey (n=104) and qualitative interviews (n=15) with people who have lived experience of chronic pain. Some final revisions were made to the toolkit content.

The feasibility and acceptability of the PAW Toolkit to employees and employers is now being tested in a cluster-randomised workplace trial, funded by the Nuffield Foundation and Versus Arthritis. PPIE is embedded at every stage of the research from development, to testing in a trial, dissemination, and informing future research. Our PPIE partner sits on our Pain-at-Work Trial Management Group and provides advice to the study team, and our Trial Advisory Board includes people with lived experience of chronic pain who review and guide us on our trial processes, research materials, dissemination and communication plans. The PPIE input in this programme of research goes beyond the immediate project and helped us to determine the key advantages and challenges of web-based interventions for training and health behaviour change. We used this knowledge (alongside that gathered in other web-based workforce studies) to develop the WWHIDE Framework: "A Web-based Workforce Health Intervention Development and Evaluation Framework". This is the first framework to present key considerations around the recruitment of employers and employees, intervention design and development, delivery modality, comparison groups for trials, intervention engagement, attrition rates, and user acceptance. Insights from our PPIE partners

and contributors will therefore inform the design of future health research studies involving web-based interventions for education, training, and behaviour change.

This project would not have been possible without PPIE input from the outset, it was vital to the success of the project, and importantly, the value of the toolkit in the real world. To produce a resource that is accessible and relevant to PwA (and others with chronic or persistent pain) requires partnership working and co-creation. The aim of the toolkit is to equip people who have pain with the knowledge, skills and confidence to effectively self-manage a painful condition at work, access help and support, enjoy a better work experience, and remain in the workforce. We will be able to provide more details about the acceptability of the toolkit, people's views towards it, and how people used it in the context of work, when our trial ends in November 2025.
We hope that involving PPIE contributors in our research will have benefits for them, as well as for research recipients. Our PPIE partner, Victoria, shared her experiences of being involved in research at the Nottingham Biomedical Research Centre Musculoskeletal Virtual Conference on Friday 25th February 2022 (available on YouTube, PPIE Session, appearing 2:35:40).