UKRI, Versus Arthritis and Eli Lilly invited proposals to establish a pain research data hub in partnership with Health Data Research UK. The purpose of the hub is to bring together and curate health data from the NHS, social care and research (academic and industry) to provide innovative new high value data resources for pain research and innovation. The aim for this hub is two-fold; firstly, it will work to bring together, curate and improve existing data sets that are valuable to the chronic pain research community. Secondly, the data hub will be central to all data and results generated from across the APDP investments, including the large consortia and research programmes. The pain research data hub will provide a key national resource for the pain research community to tackle the long-term research challenges in understanding the complexity and unpredictability of pain and reveal new and improved treatments across diverse chronic and debilitating pain conditions. The Panel assessed applications on 26 March 2021 and made one award.

Funded proposal

**Professor Emily Jefferson, University of Dundee, Alleviate: The APDP Pain Research Data Hub, University of Dundee (MR/W014335/1, 36months £2.0M)**

Co-Investigator Professor Lesley Colvin (University of Dundee)
Co-Investigator Professor Tim Hales (University of Dundee)
Co-Investigator Professor Blair Smith (University of Dundee)
Co-Investigator Mr Richard James Walls (University of Dundee)
Co-Investigator Professor David Bennett (University of Oxford)
Co-Investigator Professor Irene Tracey (University of Oxford)
Co-Investigator Professor Edmund Keogh (University of Bath)
Co-Investigator Professor Christopher Eccleston (University of Bath)
Co-Investigator Dr Philip Quinlan (University of Nottingham)
Co-Investigator Professor Ana Valdes (University of Nottingham)
Co-Investigator Professor Dorothee Auer (University of Nottingham)
Co-Investigator Professor Victoria Chapman (University of Nottingham)
Co-Investigator Professor Weiya Zhang (University of Nottingham)
Co-Investigator Professor Frances Williams (King's College London)
Co-Investigator Professor Andrew Rice (Imperial College London)

**Patient Insight Partners:**

Antony Chuter
Jillian Beggs

Our vision for the Alleviate Hub for Pain is to:

- Transform existing UK pain datasets to be Findable, Accessible, Interoperable and Reusable (FAIR)
- Link these datasets with expert data engineering, integrated into the Health Data Research (HDR) UK Gateway
- Catalyse responsible and trustworthy analysis by international researchers and innovators

Our UK-wide consortium will deliver world class health data infrastructure and services for pain research, guided by leading experts in pain research and in partnership with the NHS, Advanced Pain Discovery Platform (APDP) consortia, people with lived experience of chronic pain (PWLE) and industry. This consortium has a common desire and a commitment for change to a "data as infrastructure" approach. The fact that custodians of diverse datasets have chosen to join our consortium is testament to the need to develop new improved, more efficient methods of bringing everyone together under a common approach. Alleviate will engage directly with PWLE to maximise
impact and patient benefit. We have already held our first 'In-Principle' meeting with 9 representatives, from diverse backgrounds, with 2 PWLE co-leading the Public and Patient Involvement and Engagement Work Package.

The Dundee Health Informatics Centre (HIC) has considerable data engineering expertise and has provided leadership in health data science and research services for over a decade. Using a secure ISO27001 certified Trusted Research Environment (TRE)/Safe-Haven (where data security and safety is guaranteed) managed by HIC, Alleviate will:
- Leverage existing open-source software and infrastructure to curate and manage data (research cohorts and routinely collected health (and social) care data), streamline access and support governance
- Provide a modern, secure, and flexible design, benefitting from HIC's secure, scalable hybrid cloud 'Next-Generation' infrastructure; supported by cloud computing expertise from Amazon Web Services (AWS), enhancing an existing successful partnership
- Support analysis of multi-modal data using artificial intelligence and machine learning (e.g. epidemiological, clinical, population health, genomics, imaging, psychological, social, biological)
- Deliver a hybrid model of data access and management, i.e. supporting UK-wide data federation combined with a centralised model (Figure.1). The model will also support international datasets in the future
- Enable pain research datasets and registries, facilitating their curation and further collaboration, linking with other HDR UK Hubs, related clinical datasets (e.g. mental health, cancer) and boosting their power and discovery potential for patient benefit

Our consortium has a considerable track record:
- Specific expertise in multi-centre pain-related data
- Leading academics in pain research covering the range of data modalities across biological, psychological and social factors that influence pain. Our Co-I's are leading applicants in 4 separate APDP consortia bids
- Experience in collaborating between clinical researchers, PWLE, laboratory scientists and data scientists at local, national and global level
- Experience as a data processor for several health boards, Scottish Government, and many UK and international research cohorts
- Custodians of a TRE for secure analysis of health data at scale
- Leading many HDR UK initiatives: Phenomics portal, Scottish Data Federation, Multiomics project, Biorepository management software, Imaging, open Connector, ATLAS
- Enabling c.900 national and international research projects as a service provider (c.5years)
- 'Big-data' pipelines for efficient operation including omics to explore the biopsychosocial model of chronic pain
- Experience of building research networks and with ready access to the UKCRC Tissue Directory and Coordination Centre of over 200 biobanks

**APDP Multidisciplinary Consortia for Data Generation**

*Wave 2 Strategic Priorities Fund Call*

UKRI, Versus Arthritis and Eli Lilly invited proposals to their £14m call for large and ambitious multidisciplinary consortia. As part of a major £24m initiative to establish an Advanced Pain Discovery Platform that is jointly supported by the UKRI Strategic Priorities Fund and Versus Arthritis, the aim of this call is to build the foundation of a national-scale programme supporting discovery and
translational science that will bring together leadership, tools and resources to help unravel the complexity of pain and lead to step changes in the understanding and treatment of chronic pain across a wide range of conditions. The Panel assessed applications on 24-25 March 2021 and made four awards.

**Funded proposals**

**Professor David Bennett, University of Oxford, (MR/W002388/1, 48 months, £3.6M)**

**MICA: Partnership for Assessment and Investigation of Neuropathic Pain: Studies Tracking Outcomes, Risks and Mechanisms (PAINSTORM)**

Principal Investigator Professor David Bennett (University of Oxford)
Co-Investigator Professor Irene Tracey (University of Oxford)
Co-Investigator Dr Annina Schmid (University of Oxford)
Co-Investigator Dr Kathryn Martin (University of Aberdeen)
Co-Investigator Professor Andrew Rice (Imperial College London)
Co-Investigator Professor Blair Smith (University of Dundee)
Co-Investigator Professor Lesley Colvin (University of Dundee)
Co-Investigator Professor Douglas Steele (University of Dundee)
Co-Investigator Professor Geert Crombez (Ghent University)
Co-Investigator Dr Whitney Scott (King's College London)
Researcher-Co-Investigator Dr Abirami Veluchamy (University of Dundee)
Researcher-Co-Investigator Dr Georgios Baskozos (University of Oxford)
Researcher-Co-Investigator Dr Andreas Themistocleous (University of Oxford)
Researcher-Co-Investigator Dr Jan Vollert (Imperial College London)

**Patient insight partners:**

Lynn Laidlaw
Fiona Talkington
Jo Josh
Gordon M. Liddle

**Summary:** This consortium brings together experts in Neuropathic pain (NeuP). NeuP affects 8% of the population and is caused by damage to the sensory nervous system (through conditions such as diabetes, chemotherapy and HIV). It is increasingly common as a consequence of the ageing population, increasing levels of diabetes and enhanced cancer survival.

NeuP has a major negative impact on quality of life. Unfortunately, current management options are inadequate as they are only effective in a small subgroup of patients. Additionally, whilst NeuP impact is multidimensional, most research and clinical management in this area is separate rather than being interdisciplinary. They over emphasise pharmacological approaches, often associated with side effects, rather than taking a more holistic approach addressing the complex social and psychological aspects of NeuP.

To rectify this situation, we need to understand the mechanisms driving NeuP in patients. In order to do so, PAINSTORM will use a broad range of approaches cutting across traditional disciplinary boundaries, to uncover the causes of NeuP and understand how they interact.

This inter-disciplinary collaboration will include people living with NeuP (embedding patient and public involvement), scientists from diverse clinical and scientific backgrounds, and industry expertise to help translate the research into effective, multifaceted interventions.

Our focus will be on studying people at risk of NeuP and following their progress over time. We will use a number of established cohorts, as well as recruiting new participants, and harmonise outcomes with national scale community studies.
A key question is understanding why some people are severely impacted by NeuP whilst others with a similar pattern of nerve damage are not. Hence, we will identify the personal characteristics (such as age, gender and ethnicity), environmental/social and clinical factors which determine NeuP risk. We will identify and validate novel genetic risk factors for NeuP.

Tissue samples and patient-derived cells will be used to validate molecular pathways contributing to chronic NeuP and help develop blood biomarkers. These samples will be stored and made available to other researchers via a biobank. We will optimise measures to assess NeuP, including sensory profiling, application of remote monitoring and assessment of psychosocial factors to understand the impact of pain on daily activities (from self-care to work) and important conditions that are often associated with chronic pain such as depression, anxiety and poor sleep.

We will use innovative technologies, including brain, spinal cord and nerve imaging and electrophysiology, to directly assess the factors that drive NeuP. We will integrate this multi-dimensional dataset to understand the interaction between risk and protective factors. We will develop biomarkers, as a means to measure pain and how it changes over time, which can be applied to clinical practice and drug trials. We aim to improve targeting of existing therapies, as well as identifying and prioritising novel treatment targets.

We will engage key stakeholder groups including health professionals, people living with NeuP and industry at the outset and throughout PAINSTORM. Results will be widely disseminated through development of accessible databases, lay summaries, an accessible biobank and ongoing training of scientists and clinicians both within and external to our consortium to enhance impact. Our aim is that PAINSTORM should transform lives through our understanding and future interdisciplinary management of NeuP.

Professor Tim Hales, University of Dundee (MR/W002566/1, 48 months £3.0M)

Consortium Against Pain in Equality (CAPE) - The impact of adverse childhood experiences on chronic pain and responses to treatment

Principal Investigator Professor Tim Hales (University of Dundee)
Co-Investigator Dr Reecha Sofat (University College London)
Co-Investigator Dr Suellen Walker (University College London)
Co-Investigator Dr Line Caes (University of Stirling)
Co-Investigator Professor Colin Smith (University of Edinburgh)
Co-Investigator Dr Bhuvaneish Thangaraj Selvaraj (University of Edinburgh)
Co-Investigator Professor Gary Macfarlane (University of Aberdeen)
Co-Investigator Professor Lesley Colvin (University of Dundee)
Co-Investigator Professor Douglas Steele (University of Dundee)
Co-Investigator Dr Andrew Brown (University of Dundee)
Co-Investigator Professor Debajit Sen (University College London)
Researcher-Co-Investigator Dr Madeleine Verriotis (University College London)

Patient Insight Partner:

Janine Rennie, Wellbeing Scotland

Summary: Adverse childhood experiences (ACEs) include physical or emotional abuse, neglect, and domestic violence. The World Health Organisation describes ACEs as the commonest and most intense childhood stressors. About half of us may endure at least one, but children exposed to several are likely to have more health problems later in life, including chronic pain. There are links between exposure to multiple ACEs and social deprivation and the likelihood of ACE exposure is higher for boys, and for children of a young mother. Although there is good evidence that ACEs contribute to health inequalities, there is no widespread screening or systematic approach to reducing long term harms.
Reasons for this include limitations in existing assessment approaches, and little consideration of other factors that might increase vulnerability.

Our CAPE consortium will bring together people from a wide range of backgrounds—such as scientists, people with lived experience of ACE and chronic pain, clinical researchers, epidemiologists and psychologists. We will use an inclusive approach to integrate biological, psychological, social and cultural factors to understand the impact of ACE on chronic pain and how people respond to treatment. There are 5 related work packages:

1. We aim to develop a questionnaire-based assessment that captures ACEs. We will analyse current approaches to see which ones work best. Alongside this we will use people's first-hand accounts, to ensure that lived experiences of ACEs and chronic pain, are accurately reflected in our approach. Working with patient partners we will bring together this information to develop and test a new ACE questionnaire (the CAPE ACEQ).

2. The CAPE ACEQ will be used to enrich pre-existing data in large scale population research datasets, (e.g. UK Biobank). We will also collect data about pain and social interactions (adult relationships). We will link this to prescribing, health records (including mental health) to identify psychosocial factors that create vulnerability to chronic pain and adverse responses to treatment in those exposed to ACEs. We will examine whether the increased burden of chronic pain, which disproportionately affects those exposed to multiple ACEs, leads to higher levels of opioid prescribing and associated adverse events observed in deprived communities.

3. We will collect similar data on pain, its impact (mood, sleep, fatigue etc), ACEs, health and social factors from a large group of young patients suffering from a condition called juvenile idiopathic arthritis (JIA), who attend a specialist unit in London. We will be able to understand what factors lead to different pain routes and outcomes in these young people.

4. We will use brain imaging data from the existing population studies and new brain imaging from the young JIA group, to establish whether there are changes in brain structure and/or function that may be associated with the development of poor pain and prescribing outcomes in those exposed to ACEs.

5. We will seek biological markers of vulnerability or resilience to chronic pain and treatment in those exposed to multiple ACEs. For this we will study genetic factors, and test properties of brain cells, from donated samples. Participants in a population study called the Lothian Birth Cohort will be asked about their exposure to ACEs. Many have consented to donate brain tissue post-mortem and have already provided blood for the production of pluripotent stem cells. These special cells will be differentiated to form brain cells.

We anticipate that high quality evidence linking ACEs to chronic pain and treatment outcomes, combined with knowledge of mental health and social support, will provide a basis to develop individualised approaches to pain management and identify public health interventions to improve outcomes.

Professor Geoff Woods, University of Cambridge (MR/W002426/1, 48 months, £4.1M)

MICA: ADVANTAGE visceral pain consortium: Advanced Discovery of Visceral Analgesics via Neuroimmune Targets and the Genetics of Extreme human phenotype

Principal Investigator Professor Geoff Woods (University of Cambridge)
Co-Investigator Dr Michael Lee (University of Cambridge)
Co-Investigator Professor George Malliaras (University of Cambridge)
Co-Investigator Dr Ewan Smith (University of Cambridge)
Co-Investigator Dr David Andersson (King's College London)
Co-Investigator Dr Franziska Denk (King's College London)
Co-Investigator Dr Amanda Williams (University College London)
Co-Investigator Professor Andrew Horne (University of Edinburgh)
Co-Investigator Dr Athanasios Tsanas (University of Edinburgh)
Co-Investigator Professor Philippa Saunders (University of Edinburgh)

Patient Insight Partners:

Tess Harris, Polycystic Kidney Disease Charity
Nikul Bakshi, Crohn’s & Colitis UK
Judy Birch, Pelvic Pain Support Network
Lesley Booth, Bowel Research UK
Emma Cox, Endometriosis UK
Dr Federica LaRussa
Yvonne Tougher
Dr Nicholas Wood

Summary: The ADVANTAGE consortium aims to improve how we treat people with visceral diseases, such as endometriosis, colitis and kidney disease, focusing on their pain rather than just their underlying disease.

One in twenty individuals in the UK are disabled by visceral pain - approximately as many people as live in the entire country of Wales. The condition is a terrible burden for those who suffer from it: causing pain not only during the most intimate moments of their lives, but also frequently triggering unpredictable episodes of pain "flares" that can need hospital admission.

It is therefore surprising and disappointing how little we know about visceral pain; no one has systematically studied how the pain connects to the underlying visceral disease, how it relates to other health problems, and how it affects people's psychological wellbeing. Our consortium will set up a UK-wide database of visceral pain patients to address these questions. We will also study those nerves connecting inner organs to the brain to ultimately cause pain, as their exact identity is unknown. The database and biological knowledge collected will enable us to:
1) answer why people with the same visceral disease can have completely different pain experiences, including flares; 2) start looking for painkillers and therapies specifically designed for visceral pain, which although they are desperately needed do not currently exist.

Our work will be divided into various taskforces, each led by an internationally recognised expert clinician or scientist. All research will be enriched by input from patient and patient support organisations from start to finish. Our visceral pain database will enrol individuals with pain originating from the bladder, gut, lung, kidney, pancreas, uterus and vagina, and in the pelvis. It will be built on existing hospital and GP records and will be future-proof, set up to grow and recall volunteers for additional studies. We will also work closely with similar pain consortia being set up across the UK.

We will look especially for people at the extremes: those with little pain despite clear disease, and those with severe pain despite few signs of disease. We will record their pain using standard self-report methods, but also explore other ways to capture their experience; for example, using automatic sensors to record activity and physiological changes throughout the day. To find out what causes severe pain in some people, we will study the genetic and immune systems of participants. We will also examine differences between men and women, why certain conditions predominantly affect women, and the under-representation of women in some research areas, to make sure that any new treatments benefit everyone equally.

Our ultimate aim is to improve our understanding of visceral pain from the perspective of people living with the condition, so that the NHS can develop and offer patients more effective interventions and support to address the diverse nature of their symptoms and help improve their quality of life.
Christopher Edmund Keogh, University of Bath (MR/W004151/1, 48 months, £3.8M)

Psychosocial mechanisms of chronic pain

Principal Investigator Professor Edmund Keogh (University of Bath)
Co-Investigator Professor Christopher Eccleston (University of Bath)
Co-Investigator Professor Rachael Gooberman-Hill (University of Bristol)
Co-Investigator Professor Amanda Williams (University College London)
Co-Investigator Professor Tamar Pincus (Royal Holloway, Univ of London)
Co-Investigator Professor Candida McCabe (University of the West of England)
Co-Investigator Dr Elaine Wainwright (Bath Spa University)
Co-Investigator Professor Anthony Pickering (University of Bristol)
Co-Investigator Dr Anica Zeyen (Royal Holloway, Univ of London)
Co-Investigator Professor Carolyn Chew-Graham (Keele University)
Co-Investigator Professor Ernest Choy (Cardiff University)
Co-Investigator Dr Abbie Jordan (University of Bath)
Co-Investigator Dr Christof Lutteroth (University of Bath)
Co-Investigator Dr Emma Fisher (University of Bath)

Pain Insight Partners:
Colin Wilkinson
Jane Hall

Summary: (i) Aims and objectives
Pain that lasts a long time (is chronic) takes apart lives, relationships and families. Although biological signals can help understand why pain happens, they do not fully account for the experiences people have, or why pain develops the way it does. Psychological and social factors, such as thoughts and feelings, personal relationships, and lifestyle, can also affect chronic pain. However, we do not yet know which of these psychological and social mechanisms are most important, or how they combine with biological signals to affect chronic pain. Our aim is to determine the psychosocial mechanisms underpinning chronic pain. Our objective is to create a clearer account of how, and in what way, psychosocial factors (interacting with biology) affect pain: what makes chronic pain start, keep going, get better or get worse. In doing so, we will also identify ways to prevent chronic pain from happening, and reduce the negative effects that pain can have on people's lives.

(ii) Data to be collected
We will focus on how people think and feel about pain, how others affect their pain, and consider the wider social and environmental influences on pain. These psychosocial mechanisms will in turn be described in the context of physiological and biomedical dimensions of chronic pain. Our planned work involves people with pain at each stage to ensure our work is guided by the way pain affects people's lives. We will start by exploring the existing evidence, to identify what matters most, including what measures and methods best reflect lived experience. We will ask people with pain which of these factors matter most, and test them in existing large datasets. We will run new studies on the psychological and social factors that hold greatest promise. We will explore how the way people think and behave contributes to pain, and observe how people live their lives with pain. We will study the ways people adapt to live well with pain, and identify the part played in chronic pain by the factors we are interested in.

(iii) Benefits of the consortium
A consortium approach allows us to think big. It gives us a rare opportunity to change how we think about pain and how we research it. To achieve these ambitious goals, we need to bring together expertise from different scientific disciplines, alongside people with pain, and in a way that has not previously been possible. The Advanced Pain Discovery Platform (APDP) not only allows us to do this, but also offers us an unprecedented prospect of working consistently at a conceptual level, to generate data and test ideas. It also allows for cross-consortium working, to stimulate and evaluate
new ideas and spot opportunities for future pain research and discovery.

(iv) Legacy and/or sustainability of the network
Our primary contribution will be to identify the psychological and social factors that are most important for understanding pain. We will develop new ways to study pain, new measures of pain and its impacts, and most importantly identify key psychosocial mechanisms of pain, showing how they work alongside biology to promote or limit pain. We will provide guidance about these psychosocial mechanisms, and place this resource within the APDP, for use by the wider interdisciplinary pain research community, including those who wish to incorporate psychosocial factors in medical epidemiological, clinical, or human genotyping studies. Through our work, and the partnerships that generated it, we will open new, broad avenues of pain research that will develop better ways to help people to live well with less pain.