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A CLINICAL ASSESSMENT TOOL TO IMPROVE THE USE OF PAIN RELIEF TREATMENTS IN KNEE OSTEOARTHRITIS

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DECLARATIONS

This is to certify that work submitted in this thesis is the result of original research. It has been conducted substantially by myself with assistance outlined below. It has not already been accepted for any degree, diploma or other qualification. All authors and works to which reference has been made are fully acknowledged.

Study design, ethical application, data collection, and general administration for the Knee Pain In the Community (KPIC) study data were conducted by the KPIC study team, including Nadia Frowd, Dr. Aliya Sarmanova, Dr. Gwen Fernandes, Dr. Joanne Stocks, Associate Professor Ana Valdes, Professor Weiya Zhang, Professor David Walsh and Professor Michael Doherty. Scientific protocols that utilised the KPIC data were designed by myself, under the supervision of Professor David A Walsh, and Professor Eamonn Ferguson, with advice from Dr Daniel McWilliams.

Study design, ethical application, data collection, analysis, writing and general administration for (i) the Expert consensus study and (ii) the CAP-Knee study were conducted primarily by myself, under the supervision of Professor David A Walsh, and Professor Eamonn Ferguson, with advice from Dr Daniel McWilliams. Professor Roshan das Nair provided expert advice on the design and analysis of the interviews conducted as part of the 'CAP-Knee' study. Dr. Richard James provided support as the second coder for interview transcripts collected for the 'CAP-Knee' study.

Study design for the Investigating Musculoskeletal Wellbeing and Health (IMW&H) study was conducted by Dr. Bonnie Millar, Dr. Daniel McWilliams, Professor Eamonn Ferguson and Professor David Walsh, with some input from myself. Ethical application, data collection and general application for the Investigating Musculoskeletal Wellbeing and Health study was conducted by Dr. Bonnie Millar. Design of the study protocol that utilised the IMW&H data was conducted by myself, under the supervision of Professor David A Walsh, and Professor Eamonn Ferguson, with advice from Dr Daniel McWilliams.

All data presented in this thesis were analysed by myself, and supervision of the thesis was undertaken by Professor David A Walsh, and Professor Eamonn Ferguson.

LIST OF PUBLICATIONS

Published Papers

Akin-Akinyosoye K, Frowd N, Marshall L, Stocks J, Fernandes GS, Valdes A, McWilliams DF, Zhang W, Doherty M, Ferguson E, Walsh DA. Traits associated with central pain augmentation in the Knee Pain In the Community (KPIC) cohort. Pain. 2018.

Akin-Akinyosoye K, Frowd N, Marshall L, Stocks J, Sarmanova A, Fernandes GS, Valdes A, McWilliams DF, Zhang W, Doherty M, Ferguson E, Walsh DA. Baseline self-report 'Central Mechanisms' trait predicts persistent knee pain in the Knee Pain In the Community (KPIC) cohort. Osteoarthritis and Cartilage. 2019.

Akin-Akinyosoye K, James RJE, McWilliams DF, Millar B, das Nair R, Ferguson E, Walsh DA. The Central Aspects of Pain in the Knee (CAP-Knee) questionnaire; a mixed-methods study of a new self-report instrument for assessing central mechanisms in people with knee pain. Osteoarthritis and Cartilage. *submitted for review*

Conference presentations

European Pain Federation Congress (**Valencia, 2019**): Central Aspects of Pain in the Knee (CAP-Knee) Questionnaire for assessing central mechanisms in people with knee pain (*Poster presentation*).

British Society for Rheumatology (**Birmingham, 2019**): Self-report central mechanisms trait predicts knee pain persistence in the Knee Pain In the Community (KPIC) cohort (*Poster presentation*).

Osteoarthritis Research Society International (OARSI) World Congress (**Liverpool, 2018**): A clinical assessment tool to improve the use of pain relieving treatments in knee osteoarthritis (*Poster presentation*).

British Pain Society Annual Scientific Meeting (**Birmingham, 2017**): Pain distribution as an indicator of central mechanisms in Knee Osteoarthritis (OA) pain (*Poster presentation, Highly Commended Abstract Rossette*).

UK-RIME Showcase (**Oxford, October 2017**): Identifying central pain mechanisms in Knee Osteoarthritis (OA) (*oral and poster presentation*).

ABSTRACT

Background: In the UK, approximately 25% of individuals aged over 55 have chronic knee pain, often due to osteoarthritis (OA). Knee pain originates from the joint due to structural changes or inflammation (peripheral mechanisms), and is often intensified by processing of afferent signals by the central nervous system (central mechanisms). Imaging and psychophysical approaches could inform the presence of underlying mechanisms within individuals with knee pain but lack feasibility within clinical settings. Feasible and validated self-report approaches that can aid identification of knee OA pain mechanisms are currently unavailable.

Objectives: [1] to generate a shortlist of self-report items which reflect traits associated with underlying pain mechanisms; [2] to select a valid set of self-report items that measure a phenotypic trait associated with pain mechanisms; [3] to investigate the ability of the newly identified items to predict 1-year pain outcomes; [4] to understand participants' interpretation of items included within the developing questionnaire to inform item revision where necessary; [5] to evaluate the psychometric properties of a newly developed mechanism-based questionnaire.

Methods: *Item generation and selection* was based on exploratory analysis of responses to shortlisted items by individuals reporting knee pain (n=2152) included within the 'Knee Pain in the Community (KPIC)' cohort study. A subset of these participants (knee pain n=322, no knee pain n=98) undertook Pressure Pain Detection Thresholds (PPT) assessments at baseline. Items measuring specific traits related to pain mechanisms were selected from the survey based on expert consensus, face validity, item association with underlying phenotypes measured by originating host questionnaires, adequate targeting, and PPT correlations. An underlying trait was sought by factor analysis of the selected items.

To examine the *predictive validity* of baseline scores for the identified trait, logistic and linear regression models assessed associations with 1-year follow-up pain outcomes. Receiver-operator-characteristic (ROC) curves and areas-under-the-curve (AUC) compared the predictive strength of the identified trait to other predictors of pain outcome.

Selected items were rewritten and included within the Central Aspects of Pain in the Knee (CAP-Knee) questionnaire. Cognitive interviews across individuals with knee pain (n=22) participating within the 'CAP-Knee study' assessed participant *interpretation of CAP-Knee items*. Thematic analysis of participants' discussions for each item was used to identify emergent themes which were categorised according to whether or not they were aligned to the intended interpretation of the item. Content analysis across interview transcripts allowed coding of participant responses following Tourangeau's question response model: comprehension (completely-, partially or not completely aligned), retrieval (no-, partial- and complete- retrieval difficulty), judgement (certain initial or uncertain initial judgement) and response formulation (consistent or inconsistent).

Items were rewritten and retested in another group of interviews if (i) a mixture of aligned and not aligned themes emerged from discussions for an item, and ii) >15% of participants provided responses related to codes of poor item function, including complete non-alignment, complete retrieval difficulty, uncertain initial response and no response consistency.

Psychometric properties of the CAP-Knee were assessed in 250 community-based individuals with knee pain, of whom 76 completed the CAP-Knee twice over one month to measure repeatability.

Results:

Item generation and selection: Eight self-report items measuring traits of anxiety, depression, catastrophizing, neuropathic-like pain, fatigue, sleep disturbance, pain distribution, and cognitive impact were identified as likely indices of central pain mechanisms. PPTs were associated with items representing each trait and with their originating questionnaires. A single factor, interpreted as "central mechanisms trait" was identified across the 8 selected items and explained variation in PPT (R^2 = 0.17) better than did any originating questionnaire (R^2 = 0.10-0.13).

Predictive Validity: The central mechanisms trait score significantly predicted year 1 pain outcomes, even after adjustment for age, sex, BMI, radiographic OA severity and symptom duration (Pain persistence: RR=2.14, n=204, p=0.001; Persistent pain severity: β=0.47, n=118; p<0.002). The central mechanisms trait score showed good discrimination power in distinguishing pain persistence cases

from resolved pain cases (AUC = 0.70; n=1471). The discrimination power of other predictors, including radiographic OA (AUC = 0.62; n=204), age, sex and BMI (AUC range = 0.51 to 0.64; n=1471), improved significantly ($p<0.04$) when the central mechanisms trait was included in each logistic regression model (AUC range = 0.69 to 0.74).

Interpretation of CAP-Knee items: Participant interpretation of the final version of the CAP-Knee items was closely aligned to their intended meaning. Overall, 15 key themes were discussed by participants for items included within the CAP-Knee {One Anxiety theme = Fear; two Depression themes = Social function, Physical limitation; two Catastrophizing themes = Causes and consequences, Avoidance behaviours; two Cognitive impact themes = Task distraction, and Hypervigilance; two Sleep themes = Sleep disturbance and Use of sleeping aids; two Fatigue themes = Source of fatigue, Fatigue relief; one Pain distribution theme = Painful sites and three Neuropathic-like pain themes = Thermal allodynia, Weather induced pain and Thermotherapy. A mixture of aligned and not aligned themes emerged from discussions about the Neuropathic-like pain- and depression- items. More than 15% of participants provided responses indicative of poor item performance for the Neuropathic-like pain item only, but not the depression item.

The rewritten version of the neuropathic-like pain item was considered to work well.

Psychometric properties of the CAP-Knee: CAP-Knee displayed a wide range of scores across the study population (median 8, range 0-24). Internal consistency was acceptable ($\alpha = 0.75$) and test–retest reproducibility excellent (ICC=0.91, 95% CI, 0.86-0.94). All CAP-Knee items contributed significantly (item loading range = 0.21-0.92; $p<0.01$) to one distinct factor (CFI = 0.99; TLI= 0.98; $X^2(df)=37(20)$; RMSEA= 0.06). The CAP-Knee targeted the knee pain population well and constituted a unidimensional measure. Fit to the Rasch model was improved by item rescoring.

Conclusion: The CAP-Knee is a simple and valid self-report questionnaire, consisting of the 8 selected items which measure a single latent trait ('*central mechanisms*') in individuals with knee pain, and may help identify and target treatments that aim to reduce central sensitisation. No items associated with

peripheral mechanisms of knee OA pain were identified in this project. Future research should seek to clinically validate the stratification and prognostic characteristics of the CAP-Knee.

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LIST OF ABBREVIATIONS

ACC	Anterior Cingulate Cortex
ACR	American College of Rheumatology
ACT	Acceptance and Commitment Therapy
ARUK	Arthritis Research UK
AUC	Area Under the Curve
BMI	Body Mass Index
BRC	Biomedical Research Council
CAP-Knee	Central Aspects of Pain in the Knee
CCC	Concordance Correlation Coefficients
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CHECK	Cohort Hip and Cohort Knee
CNS	Central Nervous System
CPM	Conditioned Pain Modulation
CS	Central Seinsitization
DAMPs	Damage Associated Molecular Products
DICOM	Digital Imaging and Communications in Medicine
DIF	Differential Item Functioning
DMARDs	Disease Modifying AntiRheumatic Drugs
DTF	Differential Test Functioning
EFA	Exploratory Factor Analysis
ESEM	Exploratory Structural Equation Modelling
EULAR	European League Against Rheumatism
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
fMRI	Functional Magnetic Resonance Imaging

FPR	False Positive Rate
GCT	Gate Control Theory
GP	General Practice
GPQ	Generalized Pain Questionnaire
HADS	Hospital Anxiety and Depression Scale
IASP	International Association for the Study of Pain
ICC	Intraclass Correlation Coefficient
ICOAP	Intermittent and Constant Osteoarthritis Pain
ICVI	Item Content Validity Index
IMW&H	Investigating Musculoskeletal Health and Wellbeing
IRR	Inter-Rater Reliability
JSN	Joint Space Narrowing
K&L	Kellgren and Lawrence
KAA	Kehinde Akin-Akinyosoye
KPIC	Knee Pain and related Health in the Community
LC	Locus Coeruleus
LTP	Long Term Potentiation
MANOVA	Multivariate Analysis of Variance
MCC	Mid Cingulate Cortex
MIMIC	Multiple Causes Multiple Indicator
MOS	Medical Outcomes Study
MRI	Magnetic Resonance Imaging
NGF	Nerve Growth Factor
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NLDLA	Nottingham Logically Derived Line Drawing Atlas
NRM	Nucleus Raphe Magnus

NRS	Numerical Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
OAI	Osteoarthritis Initiative
OARS	Osteoarthritis Research Society
OARSI	Osteoarthritis Research Society International
OASIS	Observational Arthritis Study in Seniors
PACS	Picture Archiving and Communication System
PAG	Periaqueductal Gray
pc	Probability of Chance
PCS	Pain Catastrophizing Scale
PCS	Pain Catastrophizing Scale
PPI	Patient and Public Involvement
PPT	Pressure Pain Detection Threshold
PSI	Person Seperation Index
PSQI	Pittsburgh Sleep Quality Index
QST	Quantitative Sensory Testing
RCT	Randomized Clinical Trial
RGC	Reticularis Gigantocellularis
RJ	Richard James
RMSEA	Root Mean Square Error Of Approximation
ROA	Radiographic Osteoarthritis
ROC	Receiver Operating Curve
RCS	Residualized Change Score
RR	Relative Risk
RVM	Rostral Ventromedial Medulla
SD	Standard Deviation

SEM	Structural Equation Modelling
SNRIs	Serotonin- and Norepinephrine- Reuptake Inhibitors
SxOA	Symptomatic Osteoarthritis
TCAs	Tricyclic Antidepressants
TENS	Transcutaneous Electrical Nerve Stimulation
TKR	Total Knee Replacement
TLI	Tucker Lewis Index
TNF	Tumour Necrosis Factor
TNR	True Negative Rate
TPR	True Positive Rate
TS	Temporal Summation
UK	United Kingdom
US	Ultrasound
WDR	Wide Dynamic Range
WLSMV	Weighted Least-Squares Means and Variance
WRMR	Weighted Root Mean Residual

1. INTRODUCTION

1.1. Thesis Overview

Worldwide, osteoarthritis (OA) is the most common joint disease, with the knee being by far, the most commonly affected joint (Neogi, 2013). Knee OA is a leading cause of chronic pain, disability and loss of quality of life (Ma, Chan, & Carruthers, 2014). While many structures within the knee joint, such as osteophyte formation (peripheral mechanisms) have been proposed to generate OA pain (Felson, 2005), the exact aetiology of knee OA pain is not well understood (Arendt-Nielsen et al., 2015).

Other processes outside the painful affected knee (central mechanisms) have been proposed to augment knee OA pain (O'Neill & Felson, 2018). Approaches currently exist to measure these mechanisms, and are based on individuals with distinct observable traits (phenotypes) (Kittelson, Stevens-Lapsley, & Schmiege, 2016). However, the current approaches which may inform mechanism-based patient subgrouping for treatment purposes (such as Quantitative Sensory Testing, and brain imaging) are typically expensive, time consuming and not feasible within clinical settings (e.g. General Practices) (Lemmers, van Lankveld, Westert, van der Wees, & Staal, 2019; Uddin & MacDermid, 2016). Thus, there is need for a questionnaire to identify subgroups of individuals with knee OA pain, based on clinically presented phenotypes linked to the underlying mechanisms. In order to bridge this gap, this thesis seeks to develop a self-report measure for use in mechanism-based subgrouping of individuals reporting knee OA pain within clinical settings.

This chapter opens by providing an overall definition of pain and discusses the current pain theories that guide knee OA pain management (Chapter 1.2). Knee OA as a condition is then described, and the normal knee is compared to that of an osteoarthritic knee, to identify pain generating structures within the osteoarthritic knee (Chapter 1.3). Focus is further directed towards the underlying pain mechanisms that play a role in processing sensory input from the affected knee, and integration with processes within the central nervous system (CNS) - (Chapter 1.4). Objective and self-report phenotypes currently applied for identification of these pain mechanisms are narratively reviewed

(Chapter 1.5). This chapter concludes by highlighting the need for a feasible stratification tool, to enable identification of these pain mechanisms with an aim to aid, and improve, treatment of knee OA pain (Chapter 1.6).

Methods described in Chapter 2 are employed across the thesis. The first of the results chapters describes item generation from a large item pool (Chapter 3). Selection of the most representative item for each trait associated with a measure of underlying pain mechanisms are described in Chapter 4. The predictive validity of the selected items are assessed (Chapter 5) and interview approaches are conducted to revise the selected items (Chapter 6). The final version of the developed questionnaire is assessed psychometrically within a knee pain population (Chapter 7). These study findings and their implications to the existing literature are further discussed within the final chapter of the thesis (Chapter 8).

1.2. Pain

Pain, according to the International Association for the Study of Pain (IASP, 1979), is "*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*". This definition of pain incorporates the biological ("*actual or potential damage*") and psychological ("*unpleasant emotional experience*") components of pain. Whilst widely used and accepted, controversies exist about this definition, and the strengths and weaknesses of this definition are highlighted across the rest of this chapter.

Pain is typically chronologically characterised as either 'acute' or 'chronic' in nature.

Acute pain is self-limited as it is typically generated from the activation of neurophysiological pathways by noxious stimuli (nociception), linked to a specific disease or injury (Grichnik & Ferrante, 1991). For example, acute knee pain may occur as a result of fractures or sprains to structures within the knee, such as cruciate ligaments. ***Chronic pain*** is pain that persists beyond the normal time of healing (Merskey, 1986), however, the meaning of 'normal time' is not clearly described within the literature and varies across diseases. Whereas acute pain is functional and can be considered a mainly physiological response to tissue damage, chronic pain involves psychological and behavioural mechanisms in addition to physiological mechanisms

(Hasenbring, Hallner, & Klasen, 2001). Chronic knee pain may occur as a result of arthritis within the affected knee.

Management of knee OA pain in healthcare settings is based on the biopsychosocial model of pain which attributes disease outcome to the intricate, variable interaction of biological factors (genetic, biochemical, etc.), psychological factors (mood, personality, behaviour, etc.) and social factors (cultural, socioeconomic, etc.) (Engel, 1981). The biopsychosocial model attempts to incorporate within one model, previously proposed conceptual theories of pain, from the specificity theory of pain to more advanced neuromatrix theories of pain (Gatchel, Peng, Peters, Fuchs, & Turk, 2007). For the purpose of this thesis, the summaries provided are not an exhaustive account of the theories that have been proposed in the literature, but constitutes an overview of the theories that drive our current understanding and management of pain.

1.2.1. Biological Theories of Pain

Historically, 19th and 20th century theories of pain followed the traditional biomedical model of disease, which embraced a dualistic perspective of the mind and body functioning separately and independently of one another.

Originally, pain was postulated within the **specificity theory** (Descartes, 1972), to originate from a thin filament extending directly from the periphery (i.e. the site of injury), to the brain. This theory of Specifity failed to account for integrating structures within the CNS that respond to both nociceptive (caused by damage to body tissue) and non-nociceptive stimuli. The **intensity theory** proposed by Erb (1874) further conceptualized pain, not as a unique sensory experience, but rather as an emotion that occurs when a stimulus is stronger than usual (Chen, 2011). Evidence which demonstrated the existence of sensory receptors (nociceptors) which respond specifically to noxious stimuli disputed this intensity theory (Sherrington, 1906). However, advancement of the intensity theory by formed the basis for further neurophysiological models of pain, discussed below.

1.2.1.1. The Gate Control Theory, GCT (Melzack & Wall, 1965)

The GCT proposed that impulses from nociceptive fibers are transmitted to cells, which act as a gate within the substantial gelatinosa of the dorsal horn,

and project towards the brain (Melzack & Wall, 1965). Transmission occurs via nociceptors located within the periphery and involves the dynamic action of brain processes. These cells located within the dorsal horn of the spinal cord are the first transmission cells within the CNS. These cells activate neural mechanisms consisting of systems responsible for response and perception.

The GCT provided a physiological framework for understanding how peripheral excitation and central inhibition function together in the physiological expression of pain. However, the GCT is not able to explain several chronic pain problems, such as phantom limb pain, which require a greater understanding of mechanisms occurring in supraspinal regions (e.g. the brain).

1.2.1.2. The Neuromatrix Theory (Melzack & Casey, 1968)

This theory advances the GCT by focusing on supraspinal regions, and postulates that pain is a multidimensional experience produced by characteristic "neurosignature" patterns of nerve impulses generated by a widely distributed neural network (the body-self neuromatrix) in the brain (Melzack & Casey, 1968). According to this theory, the cognitive-evaluative dimension of pain is proposed to primarily influence affective and sensory dimensions of pain (Melzack & Casey, 1968). Based on the proposed dimension of cognitive evaluative aspects of pain, one can question whether the previously provided IASP definition of pain (IASP, 1979) satisfactorily captures key features of pain as a definition should. Omission of the cognitive component seems particularly important, as interpretations of the meaning and limitations of one's pain experience as determined by memory, ongoing thoughts and coping strategies, are very important features in the pain experience.

The neuromatrix theory of pain supports the multidimensional nature of pain, and is an important step in better defining supraspinal influences on pain perception (Keefe, Lefebvre, & Starr, 1996). However, the neuromatrix theory of pain is not a testable framework due to an inability to manipulate or measure all the parameters involved. The concept of a pain matrix is not meant to suggest a rigid regulatory pathway, but rather conceptually represents a collection of brain regions that are involved in neurological

functions, including, cognition, emotion, motivation, and localisation, as well as pain (Ossipov, Dussor, & Porreca, 2010).

Overall, there are also concerns that biological pain theories focus on cutaneous pain alone, and do not address issues pertaining to deep tissue, visceral, or muscular pains. Earlier biological pain theories have also received criticism due to their failure to recognize the influence of psychosocial factors, and their interactions with the pathophysiology of chronic pain. Subsequent physiological research based on the GCT and neuromatrix theory have however demonstrated that psychological factors can indeed modulate pain perception (Carroll & Edelstein, 2006).

1.2.2. Psychosocial Theories of Pain

Psychological theories of pain imply a person-centred approach and posit that each individual needs to be treated according to their own personal situation (Linton & Shaw, 2011). The IASP definition of Pain (1979) has served psychology well, and emphasizes the complexities of psychological experiences. Fortunately, recognition of psychological components encourages interventions designed to alleviate psychological states. The theories described below discuss factors which are relevant to chronic pain conditions, and are relevant to the scope of this thesis.

The **theory of 'fear-avoidance'** highlights catastrophic thinking, fear and hypervigilance as key factors within the pain experience (Lethem, Slade, Troup, & Bentley, 1983). The basic concept underpinning this theory is that: across individuals experiencing pain, avoidance leads to the maintenance or amplification of pain related fear, which in turn results in disuse and disability (Lethem et al., 1983). While a trajectory followed by individuals experiencing acute pain was described in this theory, the proposed causal links between each of the key factors are not currently empirically proven, and need further evidence for confirmation (Leeuw et al., 2007; Wideman et al., 2013).

The **theory of 'diathesis-stress'** takes into consideration both predisposing characteristics of people and an instigating event (Turk, 2002). Previous work suggests that anxiety-sensitivity serves as a vulnerability factor which predisposes individuals to pain catastrophizing (Andersen, 2012). However, the exact mechanisms through which anxiety sensitivity seems to play an

important role in exaggerated pain perception and in exacerbating avoidance behaviours are not clear.

Social cognitive theories propose that behaviour is influenced by social and psychological determinants, thus unlike the above theories, takes into account how social constructs might influence the pain experience (Norman & Connor, 1996). Social factors may further explain the pain experience in individuals and might more readily address human needs (Craig, 2009). Work demonstrating interactions between psychological factors, and social factors in individuals experiencing pain are scarce (Miró, de la Vega, Gertz, Jensen, & Engel, 2019). Other social factors, such as cultural influences, have been proposed to influence the pain experience (Campbell & Edwards, 2012; Peacock & Patel, 2008).

A broader macro perspective which truly encapsulates social factors is desirable because it could enhance dissemination of the research-based knowledge and address transformations in public policy, leading to systematic changes in the health care delivery system (Blyth, Macfarlane, & Nicholas, 2007; Poleshuck & Green, 2008; Skevington & Mason, 2004).

1.2.3. Summary

The biopsychosocial model is an advancement from the strictly biochemical perspective of pain. Evidence utilizing the biopsychosocial approach have shown superiority over simpler biomedical perspectives in predicting pain and behavioural responses to knee pain (Hunt, Birmingham, Skarakis-Doyle, & Vandervoort, 2008). As well as the factors discussed within the theories introduced above, a variety of many other factors exist which may explain the pain experience. However, this thesis does not seek to create a questionnaire with an exhaustive set of questions linked to each of the factors introduced above, but to create a parsimonious question list related to factors which are relevant to knee OA pain mechanisms. This chapter later describes the relationship between factors linked to biopsychosocial model of pain, and mechanisms associated with knee OA pain. First, knee OA as a condition in its own right is discussed below.

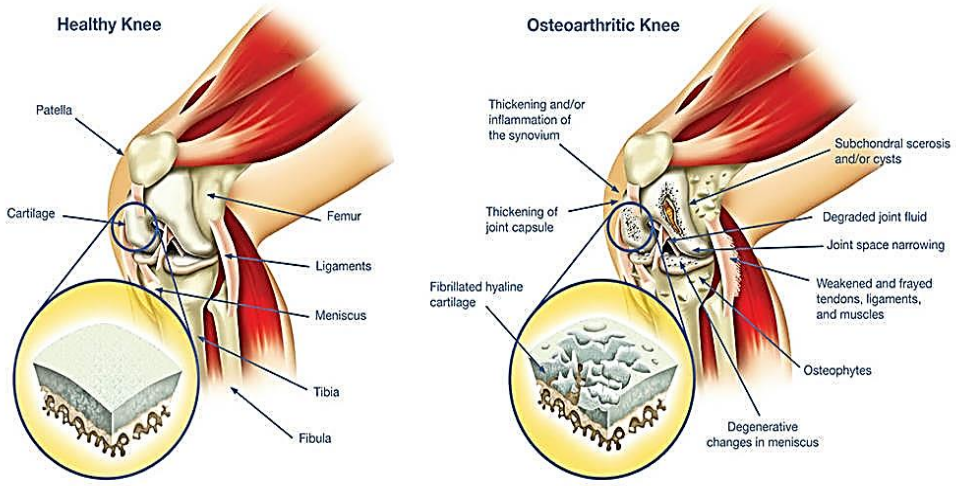
1.3. Knee OA

OA is the result of mechanical and biological events within joints, which destabilise the normal process of degradation and synthesis of articular cartilage, extracellular matrix, and subchondral bone (Sharma, Kapoor, & Issa, 2006). Animal models result in morphological changes that are similar in pathology in OA in humans, although, differences in time of disease onset and speed of disease progression may exist (Bapat, Hubbard, Munjal, Hunter, & Fulzele, 2018).

Structural differences within the osteoarthritic knee, compared to the healthy knee, is a key aspect for diagnosing this condition in individuals. The knee is a large synovial joint formed between the distal end of the femur, proximal end of the tibia and the patella. The knee allows flexion and extension, limited rotation and endures considerable mechanical stress. Smooth movement and joint cushioning is provided by the lining of the articular cartilage across the ends of the femur, tibia and posterior surface of the patella (Buckwalter, Mankin Hj Fau - Grodzinsky, & Grodzinsky, 2005). Non-osseous tissues in the knee (including the menisci, collateral and cruciate ligaments, bursae, tendons, and muscle) provide stability and determine the range of movement (Flandry & Hommel, 2011).

Three separate compartments make up the knee, including the patellofemoral, medial (inner) and lateral (outer) tibiofemoral compartment. OA can affect all three compartments, with the medial tibiofemoral compartment more commonly affected than the lateral compartment (Kim & Joo, 2012). The tibiofemoral joint as a whole is addressed in most studies; however, OA can occur solely within the patellofemoral compartment (Kim & Joo, 2012). As shown below in Figure 1-1, osteophytosis (bony growths, also known as osteophytes, which develop on joint margins) is typically prominent within the upper and lower poles of the patella. Bony apposition may occur between the patella and the anterior cortex of the lower femur.

Figure 1-1 Structural anatomy of a healthy knee, compared to an osteoarthritic knee.



Reproduced from (Weiland, Michaelis, Kirschbaum, & Rudolphi, 2005).

Radiographic appearance of the joint space may show severe narrowing (Joint Space Narrowing, JSN) which could result in the direct apposition of femoral and tibial bone surfaces. Subchondral sclerosis (abnormal tissue hardening due to increased bone density beneath the articular cartilage) occurs alongside cartilage loss, and is usually more pronounced on the tibial aspect of the joint. Subchondral cysts (fluid-filled space within one of the bones that forms the joint) usually occur in the tibia, rather than the femur (Dieppe & Lohmander, 2005).

1.3.1. Diagnostic Criteria for Knee OA

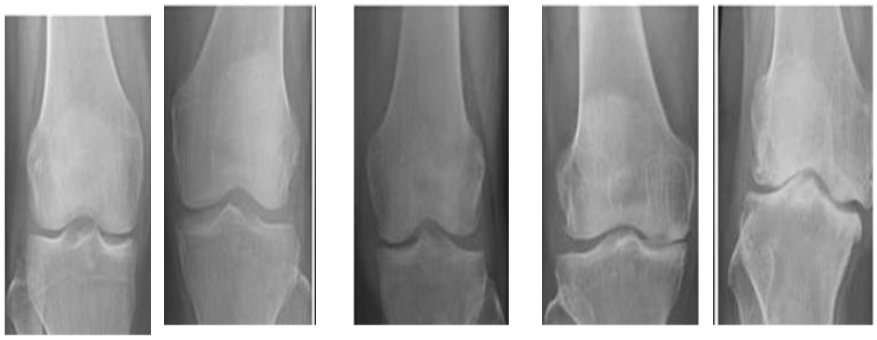
OA is broadly diagnosed by radiographic or clinical evaluation within primary healthcare and research settings.

The structural severity of knee OA is assessed primarily using conventional radiography, especially by using the Kellgren and Lawrence (K&L) grading system (Kellgren & Lawrence, 1957). Cardinal radiographic features classically used to define knee OA include JSN, osteophytosis, subchondral sclerosis, cyst formation, and abnormalities of bone contour. As shown in Table 1-1, the K&L method of radiographic grading for knee OA is a composite score combining osteophyte presence and JSN for the whole knee. Structural

abnormalities visible on radiographs, are known to appear at relatively late stages of the disease (Guermazi et al., 2013).

The K&L approach is criticized for assuming a linear radiographic progression of OA, beginning with osteophyte formation, proceeding to JSN, and subsequently leading to deformation of articular surfaces (Spector & Cooper, 1993). Therefore, according to the K&L approach, JSN in the absence of osteophyte formation cannot be measured. This translates in a lack of sensitivity of the K&L approach in individuals with knee whose radiographs show loss of cartilage, but an absence of osteophytes (Kohn, Sassoon, & Fernando, 2016).

Table 1-1 *Kellgren and Lawrence system for classification of knee OA*



Radiographic grade	0	I	II	III	IV
Classification	Normal	Doubtful	Mild	Moderate	Severe
Description	No features of OA	Minute osteophyte Doubtful significance	Definite osteophyte Normal Joint Space	Moderate joint space reduction	Joint Space greatly reduced, Subchondral sclerosis

Source: Table adapted from (Kellgren & Lawrence, 1957) and (Ryu et al., 2012).

Other radiograph scoring approaches, such as the Osteoarthritis Research Society (OARS) photographic atlas of radiographs (Altman & Gold, 2007) and the Nottingham Logically Derived Line Drawing Atlas (NLDLA) (Nagaosa, Mateus, Hassan, Lanyon, & Doherty, 2000) take changes to the joint space into account, and are becoming frequently used in clinical research. Previous work shows that the K&L is a more conservative approach for identifying

tibiofemoral OA, and suggests a lack of comparability when using either approaches (Culvenor, Engen, Øiestad, Engebretsen, & Risberg, 2015). This study showed that ROA twice was twice as common when using the OARS approach, compared to the K&L approach. No evidence compares all three methods of radiographic grading.

Radiographs show an insensitivity to progression of cartilage thinning and there are no direct means of evaluating cartilage and meniscus morphological damage from radiographs (Amin et al., 2005). However, JSN serves as a surrogate marker for these features (Adams, McAlindon, Dimasi, Carey, & Eustace, 1999; Amin et al., 2005; Gale et al., 1999; Hunter et al., 2006).

The validity of other imaging techniques, specifically ultrasound (US) techniques, have previously been reported within the literature to identify effusion, synovial hypertrophy and positive Doppler signal in individuals with knee OA pain (Sarmanova, Hall, Moses, Doherty, & Zhang, 2016). Morphological changes in bone, meniscus and femoral cartilage are assessed as single features and can be reliably evaluated using high resolution US techniques (Acebes, Romero, Contreras, Mahillo, & Herrero-Beaumont, 2013; Bruyn et al., 2016; Koski et al., 2016; Nogueira-Barbosa et al., 2015; Riecke et al., 2014; Saarakkala et al., 2012). Magnetic resonance imaging (MRI) is also considered as a sensitive imaging modality in knee OA assessment. Unfortunately, the high sensitivity provided by MRI techniques are thwarted by problems relating to practicalities and high costs.

Clinically, knee OA is defined by physical, historical, and laboratory findings. Clinical diagnosis of knee OA may be possible according to the American College of Rheumatology (ACR) criteria which allows for diagnosis based on clinical presentations alone, or clinical presentations in the presence of radiographic or laboratory presentations (Table 1-2).

Historical features include pain on motion, pain at rest, nocturnal joint pain, and morning stiffness. Features present on clinical examination include crepitus (audible grinding noise or palpable vibration), bony enlargement, malalignment, instability, effusion, expansion and limitation of motion (Baddour & Bradley, 1999; Peat, Thomas, Duncan, & Wood, 2010).

Table 1-2 ACR Criteria for the diagnosis for knee OA

Clinical	**Clinical and radiographic**	**Clinical and Laboratory**
Knee pain plus at least 3 of 6:	Knee Pain plus at least 1 of 3:	Knee pain plus at least 5 of 9:
• Age > 50 years • Stiffness < than 30 minutes • Crepitus • No palpable warmth • Bony enlargement • Bony tenderness	• Age >50 years • Stiffness < 30 minutes • Crepitus, plus osteophytes	• Age >50 years • Stiffness < 30 minutes • Crepitus • No palpable warmth • Bony enlargement • Bony tenderness • ESR <40mm/hour • RF <1:40 • SF OA
Sensitivity: 94%	Sensitivity: 91%	Sensitivity: 92%
Specificity: 88%	**Specificity: 86%**	**Specificity: 75%**

ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; SF OA, synovial fluid signs of OA (clear viscous or white blood cell count <2000/mm^3) – Adapted from (R. Altman et al., 1986).

Based on the European League Against Rheumatism (EULAR) diagnostic criteria (Zhang, Nuki, & Moskowitz, 2010), the presence of 3 symptoms (persistent knee pain, limited morning sickness and reduced function), and 3 signs (crepitus, restricted movement, and bony enlargement) can correctly diagnose 99% of radiographic knee OA cases when all 6 symptoms and signs are present (Heidari, 2011).

Less studied signs that involve clinical examination, such as instability, gait and muscle function are also frequently observed in knee OA. Questionnaire approaches have been demonstrated in previous work to correctly classify knee OA cases based on ACR clinical classification serving as the gold standard (Quintana et al., 2007; Ratzlaff, Koehoorn, Cibere, & Kopec, 2012).

1.3.2. Epidemiology of Knee OA

The prevalence of knee OA varies across studies due to different groups employing different approaches to classify the presence of OA (Pereira et al., 2011). In large epidemiological studies, OA is often defined based on standard radiographic OA (ROA) assessments, and as discuused in Chapter 1.3.1, while the KL grading approach is most often utilised, the NLDLA or OARS grading approaches are also often employed. Other studies employ clinical examinations to classify the presence of OA, knee OA is generally defined by the presence of pain, aching, crepitus and stiffness in the affected knee (Altman et al., 1986). Symptomatic OA (SxOA) on the other hand indicates the presence of both ROA and symptoms (i.e. pain, aching, and stiffness) in the same joint attributable to OA. As such, its prevalence is generally lower than that of ROA (i.e. regardless of symptoms). For example, in the Johnston country OA project, within adults aged 45 or over, prevalence was 28% for ROA, and 17% for SxOA (Jordan et al., 2007) This finding was similar in the Framingham study population (Felson et al., 1987).

Prevalence of Knee OA increases with age, and is higher amongst females compared to males. Prevalence of SxOA in the Johnson Country OA cohort was shown to double from 16.3% in the 55- to 64-year range, compared to 32.8% in the 75 plus age group (Jordan et al., 2007). SxOA has been reported to be prevalent in 10% of men and 13% of women (Zhang & Jordan, 2010).

Geographical estimates of between 5% and 16% prevalence of SxOA have been reported across various countries (Pereira et al., 2011). In England, the prevalence of knee OA ranges from around 15% to 21% (Neogi, 2013; Peat, McCarney, & Croft, 2001). The incidence of a new GP consultations for knee pain in adults aged 50 and over is approximately 10% per year in the United Kingdom (UK) (Jordan, Jinks, & Croft, 2006), with a rate of incidence reported as 2.5% in adults aged 55 and over (Cooper et al., 2000). Similar to the UK, just under 10% of the United States (US) population is diagnosed with SxOA by the age of 60 (Losina et al., 2013).

1.3.3. Risk factors for Knee OA

OA was previously attributed solely to ageing. However, other major risk factors (*surrogates for underlying causes*), found to be demographic and

mechanical in nature, associate with knee OA pain (Ingham et al., 2011; Silverwood et al., 2015; Timmermans et al., 2019). Unless risk factors are measured and controlled, any reported findings are susceptible to confounding bias (Fewell, Davey Smith, & Sterne, 2007).Where applicable in this thesis, relevant models will account for these risk factors discussed below.

1.3.3.1. Demographic risk factors

Epidemiological studies, such as the Framingham and the Chingford women's study show some convincing evidence for **age** is an associated risk factor for the incidence or progression of knee OA (Felson et al., 1987; Hart, Doyle, & Spector, 1999). Compared to younger adults, cells which secrete the matrix of cartilage and become embedded in it (chondrocytes) from older adults exhibit many of the changes that are typical of cell senescence (deterioration with age). This can contribute to a decline in chondrocyte numbers due to increased cell death, although the extent of cell death with aging or in OA has varied among studies (Loeser, 2009). Studies have demonstrated that oxidative damage induced by reactive oxygen species (ROS) mediates chondrocytes ageing (Lepetsos & Papavassiliou, 2016). In other words, while young joint tissues compensate, to some degree, to abnormal mechanical stress, the ability to compensate to stress declines with age.

Obesity and high BMI have long been recognized as potent risk factors for OA, especially medial compartment OA of the knee (Felson, Zhang, Anthony, Naimark, & Anderson, 1992). One group reported an estimated 9%-13% increased risk of the disease at the knee and hand with every kilogram (kg) increase in body mass (Cicuttini, Baker, & Spector, 1996), a finding which is consistent with an earlier study (Hart & Spector, 1993). The mechanism by which obesity influences OA is still open for debate, as it may be mostly biomechanical in origin or might involve metabolic/systemic factors (Powell, Teichtahl, Wluka, & Cicuttini, 2005).

Female sex is a strong risk factor in individuals with knee OA (Blagojevic, Jinks, Jeffery, & Jordan, 2010; Teichtahl, Wluka, Proietto, & Cicuttini, 2005).It is possible that this link might be due to higher levels of adipose derived systemic leptin concentrations in females, compared to males (Teichtahl et al., 2005). Oestrogen production in average adult female, compared to males, may partially account for the gender disparity towards OA, however, the exact

effect of oestrogen on OA is controversial. Several studies have shown a protective effect of oestrogen(Carbone et al., 2004), contradictory to other study findings (Hannan, Felson, Anderson, Naimark, & Kannel, 1990; Hart et al., 1999).

1.3.3.2. Mechanical risk factors

Knee injury has been reviewed by several studies (Fernandes et al., 2018a), with one meta-analysis demonstrating that the pooled OR for knee injury as a risk factor for OA was 2.83 (95% CI 1.91–4.19) (Silverwood et al., 2015).

Varus (bow-leg) - and valgus (knock knees) alignment are reported to increase the risk of progression of knee OA, however, varus but not valgus alignment was reported to increase the risk of incident knee OA (Sharma et al., 2010). One systematic review did report that females with knee OA appear to have more varus-valgus laxity than males, which might explain previously reported associations between varus-valgus laxity and knee OA (Freisinger, Schmitt, Wanamaker, Siston, & Chaudhari, 2017).

1.3.3.3. Lifestyle and genetic risk factors

One meta-analysis by Silverwood et al., (2015) showed no statistically significant risk for smoking (Pooled OR = 0.92; 95% CI = 0.83 – 1.01, I^2 = 43.6%). Debate exists for the role of occupational activity, physical activity, comorbidities, education and household income, as risk factors for Knee OA (For Review- See Silverwood et al., 2015).

Several studies also support the genetic effect of genes linked to joint development (GDF5), and inflammation (IL1RA) on risk of OA (Valdes & Spector, 2011). Significant levels of leptin (*a product of the obesity gene*) were observed in the cartilage and osteophytes of people with OA, whereas few chondrocytes produced leptin in the cartilage of healthy people (Teichtahl et al., 2005).

1.3.4. Burden of Knee OA

Knee OA is a very common disease and typically manifests as knee pain in older individuals (Hunter & Bierma-zeinstra, 2019). Knee OA has a significant impact on the individual due to the pain experienced, as well as affecting the individual's psychosocial and physical function (Hunter & Bierma-zeinstra,

2019). Knee OA is known to be the leading cause of disability in later life, and is set to have an increased economic burden as the population ages.

The cost of OA to society is also significant and related to its high prevalence. Currently, the economic burden of OA is evident in its costs to healthcare, either directly (*represented by pharmacological/non-pharmacological treatments, surgery, use of resources and management of complications due to OA*), or indirectly (*represented by loss of time from work, decreased productivity because of pain, care-giver time, premature mortality and disability compensation/benefits*) (Chen, Gupte, Akhtar, Smith, & Cobb, 2012). One group reported that in the UK, direct costs for topical and oral NSAIDs for OA were estimated to be £19.2million and £25.65million, respectively (Chen et al., 2012). This group also reported indirect costs of OA caused a loss of economic production of over £3.2billion, with £43million spent on community services, and £215million spent on social services for OA (Chen et al., 2012).

Other reports from the US, demonstrated annual cost of job-related OA due to costs (e.g. time taken off work) to be between $3.41billion to $13.23billion (Kotlarz, Gunnarsson, Fang, & Rizzo, 2010; Leigh, Seavey, & Leistikow, 2001). The authors report that the cost of OA to the job sector costs exceeds costs due to pulmonary diseases, or renal and neurologic diseases combined (Leigh et al., 2001). Intangible costs (*such as out-of-pocket costs, loss of earnings due to changes in occupation and domestic roles*) are not often estimated in studies, and future research is needed in this area to truly reflect the disease burden.

1.4. Knee OA pain

Pain is a prevalent symptom in OA, occurring much more commonly than stiffness or disability. The current focus of medical intervention for knee OA is on systemic pain relief, given that no cure exists for the disease. It is therefore important that treatment of knee pain is a key focus during the management of knee OA. However, as with all kinds of pain, knee OA pain is a condition where all dimensions of pain should be considered during patient management. The rest of this thesis focuses on knee OA pain, in an attempt to highlight the mechanisms that drive knee pain, and ways in which to effectively provide treatment based on targeting these underlying knee OA pain mechanisms.

1.4.1. Nature of knee OA pain

Knee OA pain is a “pathophysiological nociceptive pain” which occurs when the tissue is inflamed or injured (Schaible & Richter, 2004). Osteoarthritic features within the affected knee (described in Chapter 1.3.1), have been linked to knee pain (Dieppe, 2004; Kinds et al., 2011). People with clearly abnormal joint radiographs may have no pain, or only mild pain, whereas others with pain may not have ROA (Bedson & Croft, 2008; Finan et al., 2013). One systematic review showed that 15%-76% of individuals with knee pain had radiographic features of OA (e.g. osteophytes, JSN), and 15%-81% of subjects with ROA had knee pain (Bedson & Croft, 2008).In older studies, such discordance is considered to be less in the presence of severe stages of radiographic disease (Felson et al., 1987; Hochberg, Lawrence, Everett, & Cornoni-Huntley, 1989). In a more recent study, a strong dose-response relationship between ROA severity and knee pain (*as measured by frequency-, consistency-, and severity- of knee pain*) was observed by matching sets of two knees within individual participants whose knees were discordant for pain status (Neogi et al., 2009). This finding suggests that some of the discordance observed in the literature might be due to person confounding factors (Neogi et al., 2009).

Reports of a sustained burning pain, pins and needles, shooting paroxysmal (electric shock-like) pain, characteristic of neuropathic-like pain, have been reported across individuals with localized OA pain (Hochman, Gagliese, Davis, & Hawker, 2011; Ohtori et al., 2012; Wagstaff, Smith, & Wood, 1985). Neuropathic pain results from injury or disease of neurons in the peripheral or central nervous system (Hochman et al., 2011).

Knee OA pain has also been described as intermittent, and worse during weight bearing activities. One qualitative study demonstrated that individuals with knee OA describe two distinct types of pain: (a) a dull, aching pain that comes and goes, and; (b) a constant pain, punctuated increasingly with short episodes of a more intense, often unpredictable, emotionally draining pain (Hawker et al., 2008).

Pain patterns differ substantially across individuals, with a within-day range seen across individuals with OA (Allen, Coffman, Golightly, Stechuchak, & Keefe, 2009). A circadian rhythm of pain has been observed within patients

with knee OA (Bellamy, Sothern, Campbell, & Buchanan, 2002). Not much is known however, about the relevance of these patterns, and further research may have significant implications for clinical practice and research methodology.

1.4.2. Pain processing pathways

Sensory afferent nerve fibres carry sensory information from the periphery of the body to the dorsal horn of the spinal cord, giving rise to ascending spinothalamic tracts (Figure 1-2).

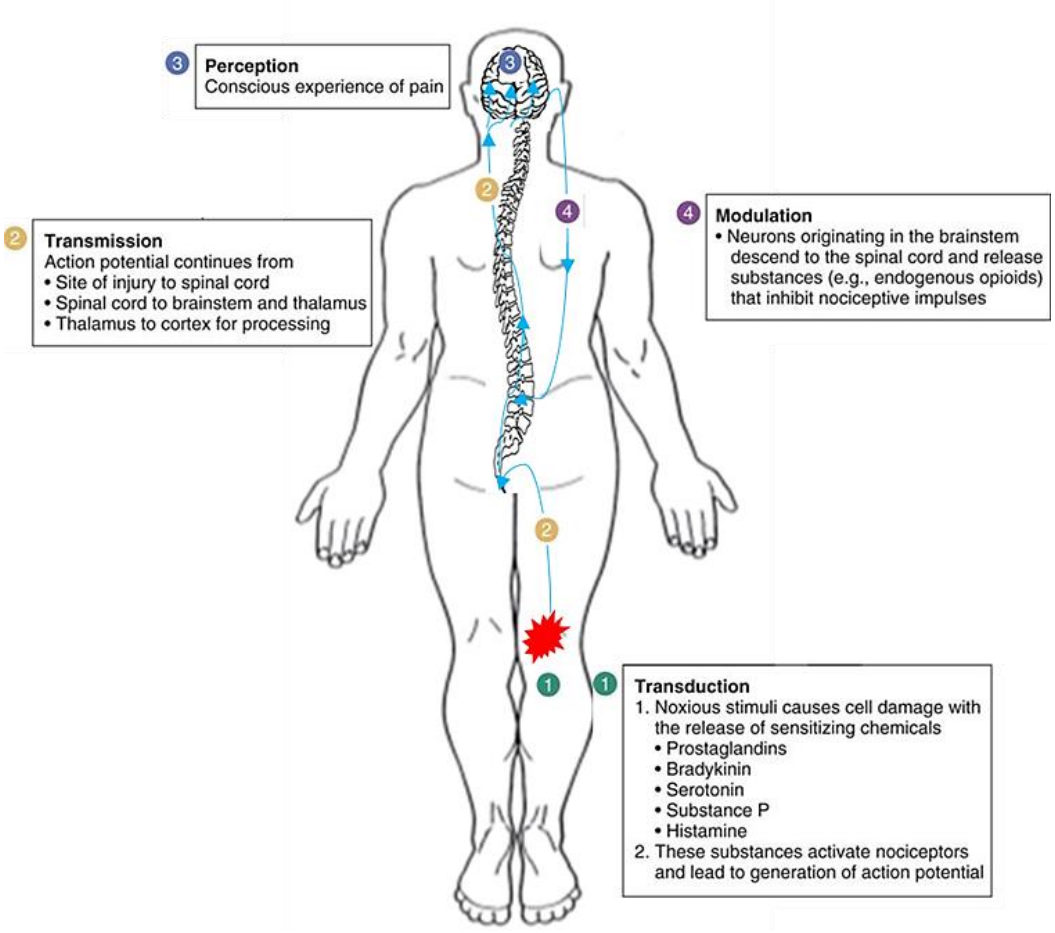
Nociceptive pain originates from the osteoarthritic knee. *1,* Transduction occurs when there is release of chemical mediators. *2,* Transmission involves the conduct of the action potential from the periphery (injury site) to the spinal cord and then to the brainstem, thalamus, and cerebral cortex. *3,* Perception is the conscious awareness of pain. *4,* Modulation involves signals from the brain going back down the spinal cord to modify incoming impulses.

The cell bodies of these afferent nociceptors are located within the dorsal horn of the spinal cord. Here, the first synapse is made with interneurons, or with supraspinal-projecting neurons, carrying pain signals to the higher regions of the neuraxis where they are ultimately experienced by the conscious brain (Miller et al., 2015).

The main ascending pathways located within the spinal cord comprises of spinothalamic tracts, with networks distributed towards brain regions, including the primary and secondary somatosensory cortex (S1 and S2, respectively), anterior- and mid-cingulate cortex (ACC and MCC, respectively), and insula (Devinsky, Morrell, & Vogt, 1995; Kenshalo & Isensee, 1983; Tracey, 2005; Treede, Kenshalo, Gracely, & Jones, 1999); all reportedly involved with pain processing and perception of pain (Figure 1-2).

Complex central processing of ascending (incoming) signals from peripheral tissues, are in turn powerfully modulated by descending inhibitory and facilitatory mechanisms within higher brain centers. As illustrated in Figure 1-2, descending pain pathways from the cortex (prefrontal cortex; anterior cingulate cortex) project to the brainstem and spinal cord. Endogenous pain inhibition at the spinal level has been suggested to occur within descending pain pathways (Bingel, Herken, Teutsch, & May, 2008).

Figure 1-2 Physiology of the knee pain experience



(Adapted from: https://nursekey.com/20-drugs-used-for-pain-management/")

This descending pain pathway includes a circuit of brain structures, including the periaqueductal gray (PAG) in the upper brain stem, the locus coeruleus (LC), the nucleus raphe magnus (NRM) and the nucleus reticularis gigantocellularis (RGc) (Bingel et al., 2008).

Although increased descending facilitation in experimental animal models has been demonstrated, how this mechanism participates in clinical conditions has not yet been demonstrated. It has been suggested that activation of putative pain facilitation cells occurs within the rostral ventromedial medulla, RVM, (Ossipov et al., 2010), but the underlying mechanisms for pain facilitation are yet to be confirmed.

1.4.3. Knee (OA) Pain Mechanisms

Knee OA pain reflects a state of altered pain processing such that everyday stimuli are perceived as being painful. Insight into the peripheral and central neurophysiologic mechanisms that modulate knee OA pain are discussed

below. While peripheral mechanisms (*pain processing within the affected knee*) play an important role in driving the knee pain experience, central mechanisms (*pain processing within the CNS*) have been suggested to be just as important. These mechanisms have only recently begun to be addressed in the context of pain treatment in knee OA and other musculoskeletal conditions. Evidence on the role of these mechanisms in knee OA pain are discussed below.

1.4.3.1. Peripheral mechanisms of knee OA pain

Peripheral mechanisms of OA pain are directly linked to its pathology within the joint and arises from the tissues, nerves, or nerve roots. Knee pain has been demonstrated by several studies to show associations with abnormalities within the affected knee, including bone attrition, bone marrow lesions, synovitis/effusion, and meniscal tears (Torres et al., 2006; Yusuf, Kortekaas, Watt, Huizinga, & Kloppenburg, 2011).

Tissue injury and tissue remodelling characteristic of OA, produces a different biochemical environment in joints than the set of molecules that facilitates normal acute pain responses (Sokolove & Lepus, 2013). Recent evidence suggests that damage-associated molecular products (DAMPs), associated with inflammation in OA (Liu-Bryan & Terkeltaub, 2015), may directly excite nociceptors (Allette et al., 2014; Liu, Xu, Park, Berta, & Ji, 2010; Marchand, 2008; Miller, Miller, & Malfait, 2014; Miller, Jung, Bhangoo, & White, 2009; Qi et al., 2011; Shibasaki et al., 2010). As a result of continued stimulation by products of tissue injury and inflammatory processes, the sensitivity of the peripheral terminals of nociceptive fibres at the affected site increases. Thus, peripheral nociceptors may become sensitized, meaning that the threshold for activation is reduced. Such sensitization to the nociceptors within the affected joint is referred to as 'peripheral sensitization'. **Peripheral sensitization** is classically defined as a process whereby the activation threshold of joint nociceptors is reduced, and afferent nerves become hypersensitive to both normal and noxious movement (Coggeshall, Hong, Langford, Schaible, & Schmidt, 1983; Grigg, Schaible, & Schmidt, 1986; Schaible & Schmidt, 1985, 1988).

Peripheral sensitization can also occur after nerve lesions. After a nerve injury, the abundance of immune and inflammatory mediators (catecholamine,

prostaglandins, histamine, serotonin, Tumour Necrosis Factor (TNF), cytokines and Adenosine Triphosphate ATP) causes peripheral sensitization (Campbell & Meyer, 2006). Other explanations for neuropathic origins of peripheral sensitization might be that areas of nerve injury may be tethered to moving structures (e.g., tendons). If this is indeed the case, otherwise normal movements may evoke an increase in pain by possibly activating nociceptors (Campbell & Meyer, 2006). Nerve Growth Factor (NGF), is an important regulator of function, differentiation, growth, survival and death of neurons. NGF has been found to be elevated during inflammation (Hefti et al., 2006), and suggested to influence an increase in inflammatory mediators in animal models of OA (Ivanavicius et al., 2007). The role of NGF in maintaining structural and functional neuronal integrity suggests that perhaps following neuronal injury, raised NGF levels may be associated with the development of a neuropathic knee OA pain. It is also possible that intact nociceptors which survive injury due to osteoarthritic damage may influence the onset of neuropathic pain (Campbell & Meyer, 2006).

Evidence from primate and rodent models demonstrate that peripheral nerve lesions lead to spontaneous activity developing in uninjured, unmyelinated nociceptive afferents that share the same innervation territory as the transected fibres (Ali et al., 1999; Djouhri, Koutsikou, Fang, McMullan, & Lawson, 2006; Wu et al., 2001). These findings must be interpreted with caution as extrapolation of data from animal models of OA to the human condition needs more precision. There is also room for advancement in understanding the specific pathological peripheral processes that drive nociceptive or neuropathic OA pain. Understanding the contributions of nociceptive fibres, whether injured or uninjured, in the generation of different pain patterns (described in Chapter 1.4.1.) remain unanswered.

1.4.3.2. Central mechanisms of knee OA pain

Peripheral sensitization adds significantly to the influx of nociceptive input to the spinal cord (McDougall, 2006; Schaible, 2007).

Central mechanisms of OA pain are operationally defined as those processes occurring within the CNS. Such mechanisms might include for example, spinal nociceptive transmission, central sensitization, and production or modulation of conscious pain (sensory-discriminative, cognitive evaluative and affective-

motivational aspects of pain response) within specific brain areas – described previously in Chapter 1.4.2. The specific central mechanisms which have been linked to knee OA pain are described in more detail below.

Central Sensitization/Spinal Hyperexcitability

The IASP defines central sensitization (CS) as the "increased responsiveness of the nociceptive neurons in the CNS to their normal or subthreshold afferent input" (Turk, 1987). In essence, higher order neurons in the spinal cord become hyper excitable. It is important to consider, however, that while pain perception is easily measured in humans, it is not currently possible to directly measure activity of the nociceptive neurons.

There is evidence that inflammatory mediators contribute to sensitization of the spinal neurons, furthering the relationship between inflammatory response and central sensitization (Moalem & Tracey, 2006; Orita et al., 2011). Long-term potentiation (LTP) within the synapse (*a junction of two neuronal fibres where impulses pass by diffusion of neurotransmitters*) is another activity-dependent mechanism suggested to drive CS. LTP is described as a persistent increase in synaptic strength which is dependent on high frequency stimulation following brief delivery of a high-frequency train of stimulation. LTP may exist within one synapse (*homosynaptic*) or several synapses (*heterosynaptic*). Homosynaptic LTP occurs at the synapse between the nociceptor and dorsal horn neuron (von Hehn, Baron, & Woolf, 2012) and involves an exaggeration of nociceptor responsiveness. Heterosynaptic LTP takes place at synapses not restricted to the initiating nociceptor input and is particularly prominent in CS (Vardeh, Mannion, & Woolf, 2016). This suggests that persistent input from nociceptors can enable subsequent long-lasting facilitation of responses to inputs from nociceptive fibers located at topographically different locations. Such synaptic plasticity contributing to CS exists within the spinal cord (Latremoliere & Woolf, 2009), and in other CNS regions, for example the anterior cingulate gyrus, prefrontal cortex, amygdala, and periaqueductal gray (Li et al., 2010).

Current evidence, although sparse, currently exists to link neuropathic-like pain with measures of CS in individuals reporting knee OA pain (Fernandes, Valdes, Walsh, Zhang, & Doherty, 2018b; Hochman, Davis, Elkayam,

Gagliese, & Hawker, 2013; Hochman et al., 2011; Moreton et al., 2015; Ohtori et al., 2012; Oteo-Álvaro et al., 2015). Further work is still needed to discern between the peripheral and/or central mechanisms that drive neuropathic pain in knee OA.

Dysregulation of descending and ascending pathways

Imaging studies comparing individuals with OA to controls, have highlighted the involvement of pain related brain regions, including the primary and secondary somatosensory cortices, insula, cingulate cortices, thalamus, amygdala, hippocampus and PAG in the processing of OA pain (Chen, Spaeth, Retzepi, Ott, & Kong, 2014b; Gwilym et al., 2009; Howard et al., 2012; Kulkarni et al., 2007; Lewis, Parker, Sharma, Rice, & McNair, 2018). Some of these regions reported by previous studies have been linked to the "pain matrix" (see Chapter 1.2.1.2). Evidence to suggest whether dysregulation in these regions might be involved in pain processing in OA pain is growing, but yet inconclusive and demand well powered studies (Chen et al., 2014b; Lewis et al., 2018; Mao, Bai, Zhang, Zhang, & Zhang, 2016). Understanding the interaction between higher brain sites (e.g. areas involved with emotional learning involving descending pain modulatory systems) may reveal significant insights into the central mechanisms associated with chronic OA knee pain (Ossipov, Morimura, & Porreca, 2014).

Previous work reported decreased activation in the rostral anterior cingulate cortex (rACC) and higher levels of RVM activation to punctate stimuli in individuals with knee OA pain reporting neuropathic-like symptoms, compared to those without neuropathic-like pain symptoms (Soni et al., 2016). This suggests that processing in these centrally located networks might drive neuropathic pain mechanisms.

1.4.4. Summary

Peripheral and central pain processing pathways have been suggested to modulate pain in a variety of chronic musculoskeletal conditions, including OA (Sofat, Ejindu, & Kiely, 2011). Peripheral mechanisms are clearly important in driving the OA knee pain experience. However, central mechanisms are superimposed upon the more traditional peripheral factors, thus causing mixed pain states within individuals with knee OA.

1.5. Phenotypes of knee OA pain mechanisms

Across chronic pain conditions, traits (defined as “a distinguishing quality or characteristic of behaviour, thought, and emotion” that is observable) collectively contribute to a phenotype (Kassin., 2003). Traits measured by self-report approaches (“self-report traits”), such as depression or catastrophizing, have been shown to contribute to phenotypes which predict pain and function in individuals with knee OA (Kittleson, Stevens-Lapsley, & Schmiege., 2016; Dell’Isola, Allan Smith, Marreiros & Steultjens, 2016; Deveza, Melo, Yamato, Mills, Ravi, & Hunter, 2017; Felson, 2010). Hill et al. (2008) previously demonstrated that including various psychosocial traits within a questionnaire allowed identification of an underlying phenotype of psychosocial distress in a back pain population. This thesis explores these self-report traits and their associations with knee OA pain mechanisms. Phenotypes can identify and characterize a subgroup in a defined population” (Dell’Isola, Allan, Smith, Marreiros, & Steultjens, 2016). It is possible that employing self-report phenotypes may allow identification of specific mechanisms-based subgroups of knee OA pain.

Clinical studies have used psychophysical techniques such as Quantitative Sensory Testing (QST), and imaging techniques to phenotype patients and attempt differentiation between peripheral and central mechanisms of pain in individuals with knee OA (Arendt-Nielsen et al., 2015; Gwilym et al., 2009). Current self-report approaches to identify mechanism-based subgroups across individuals with knee pain by identifying the presence of central sensitization, base the phenotypes on those seen within individuals with central sensitivity syndromes, and might neglect phenotypes specific to individuals with knee OA pain (Nishigami et al., 2018). There is also a lack of evidence to demonstrate a relationship between the existing self-report approach, and more objective measures of central mechanisms of pain across individuals. In addition, this attempt fails to identify peripheral pain mechanisms in individuals with knee OA.

A narrative review of the evidence for these mechanism-based phenotypes according to psychophysical, imaging and self-report measurement approaches (as summarized in Table 1-3), and their relation to clinical outcomes, is provided below.

1.5.1. Psychophysical phenotypes

One way to identify the underlying pain mechanisms in people with knee pain is to establish the presence of sensitization in the nervous system. QST is a methodological approach usedfor mechanism-based phenotyping of OA pain (Suokas et al., 2012), and involves assessing somatosensory evoked responses to noxious or innocuous stimuli using controlled mechanical, chemical, electrical, and/or thermal test modalities (Pavlakovic & Petzke, 2010).

QST allows assessment of cutaneous and deep tissue sensitivity to painful and non-painful stimuli (Pavlakovic & Petzke, 2010), and can be used to assess a gain in- (*hypersensitivity*), or loss of- (*hyposensitivity*) somatosensory function. Widespread hyperesthesia (*defined as increased sensitivity to stimulation, characterised as hyperalgesia and allodynia described below*) have been demonstrated across individuals with knee OA pain (Graven-Nielsen, Wodehouse, Langford, Arendt-Nielsen, & Kidd, 2012; Suokas et al., 2012). Conducting the QST battery of test is rather expensive and time consuming, but each test provides useful information on the state of peripheral sensory and pain perception, as well as central sensitization.

1.5.1.1. Hyperalgesia

Hyperalgesia is defined as increased pain from a stimulus that normally provides pain, and serves as a useful phenotypic marker of knee OA pain mechanisms. Hyperalgesia is either induced mechanically or thermally in clinical/research settings.

Primary hyperalgesia is defined as changes in the area of injury and is characterised by increased sensitivity in knee OA, possibly due to sensitization within the affected site, which may occur following inflammation within the affected knee - suggestive of peripheral sensitization (Woolf, 2011) (see chapter 1.4.3.1).

Table 1-3. Phenotypes associated with Knee OA pain mechanisms

Markers	Indicators of peripheral mechanisms	Indicators of central mechanisms
Psychophysical markers	Hyperesthesia • Increased sensitivity to mechanical stimuli at the knee (primary hyperalgesia) • Secondary hyperalgesia absent • Allodynia absent Temporal Summation (TS) • No enhanced local or distal temporal summation Hypoesthesia Absence of hypoesthesia	Hyperesthesia • Increased sensitivity to mechanical stimuli at the knee (primary hyperalgesia) and at distal sites (secondary hyperalgesia) • Allodynia may be present Temporal Summation (TS) • Enhanced TS at local and/or distal sites Hypoesthesia Thermal and/or mechanical hypoesthesia may be present

Table 1-3(Cont.). Phenotypes associated with Knee OA pain mechanisms

Markers	Indicators of peripheral mechanisms	Indicators of central mechanisms
Imaging markers	Knee imaging • Synovitis and effusion evident following ultrasound. • Radiographic OA pathology present Brain Imaging • Normal brain activity and normal grey matter volume across brain regions.	Knee imaging • Synovitis and effusion following ultrasound may be present. • Radiographic OA pathology may be present Brain Imaging • Increased activity and reduced gray matter volume within the medial and orbital prefrontal cortex, as well as bilateral accumbens, thalamus, RVM and amygdalae.
Self-report markers	Low scores on self-report measures of: • Body Pain distribution • Depression • Anxiety • Catastrophizing • Sleep disturbance	High scores on self-report measures of: • Body Pain distribution • Depression • Anxiety • Catastrophizing • Sleep disturbance

Secondary hyperalgesia, on the other hand, is the response of the CNS to such injury, resulting in enlargement of receptive fields, lower pain thresholds at unaffected sites (Kosek & Ordeberg, 2000). As discussed in Chapter 1.4.3.2, enlargement of receptive field outside of the affected knee is possibly due to heterosynaptic plasticity which is prominent in CS (Latremoliere & Woolf, 2009; Tanasescu, Cottam, Condon, Tench, & Auer, 2016).

Pressure Pain Detection Threshold (PPT) is a QST modality most commonly utilized in the assessment of mechanical hyperalgesia. Mechanical hyperalgesia has been demonstrated across individuals with knee OA at the painful knee, indicative of primary hyperalgesia (Arendt-Nielsen et al., 2010; Finan et al., 2013; Frey-Law et al., 2016; Imamura et al., 2008; King et al., 2013; Kuni, Wang, Rickert, Ewerbeck, & Schiltenwolf, 2015; Moss, Knight, & Wright, 2016; Suokas et al., 2012; Wylde, Palmer, Learmonth, & Dieppe, 2012b). Mechanical hyperalgesia has also been demonstrated extensively (secondary hyperalgesia) in individuals with OA, indicating widespread changes in the nociceptive processing system (Arendt-Nielsen et al., 2010; Fingleton, Smart, Moloney, Fullen, & Doody, 2015; Imamura et al., 2008; Suokas et al., 2012; Wylde et al., 2012b). Similarly, local and widespread thermal hyperalgesia have been reported in individuals with knee OA (Moss et al., 2016), but only for cold, not heat stimuli (Fingleton et al., 2015; Marx, Menezes, Horovitz, Jones, & Warren, 2003; Wylde et al., 2012b).

One group showed that while the degree of sensitization to mechanical stimuli correlated with self-report pain, it did not correlate with radiological findings (Neogi et al., 2015), leading to the conclusion that CS is an important, independent, contributor to knee OA pain.

1.5.1.2. Enhanced temporal summation/Wind up

Temporal summation (TS) is a normal feature of the coding properties of some wide dynamic range (WDR) neurons located within the spinal cord, and not an expression of CS. Individuals with knee OA pain however, show enhanced TS (*increased pain severity caused by repeated stimulus*) or spatial summation (*increased pain severity in response to stimuli over small area compared to a larger area*) (Arendt-Nielsen et al., 2010; Frey-Law et al., 2016; Goodin et al., 2014). This TS phenotype may be indicative of short-term mechanisms of CS, or alterations in synaptic plasticity within the CNS due to increased sensitivity

following repeat stimulation. There are also report of enhanced TS alongside other indices of CS, such as secondary hyperalgesia (Arendt-Nielsen et al., 2010; Neogi et al., 2015).

1.5.1.3. Other psychophysical approaches

CPM is a QST approach that assesses the efficiency of the endogenous pain modulation system within the CNS (previously discussed in Chapter 1.4.2), which has been reported to be impaired in individuals with OA (Imamura et al., 2008; Ji, Kohno, Moore, & Woolf, 2003; Kosek & Ordeberg, 2000; Kuni et al., 2015). There is need for evidence to disentangle the relationship pain modulation paradigms and other top-down pain-regulating mechanisms, including cognitive and emotional factors such as stress and anxiety.

Local and extensive allodynia (*defined as pain due to stimulus that does not normally provoke pain*) have been described in patients with painful knee OA, compared to controls (Hendiani et al., 2003; Kavchak et al., 2012). **Hypoesthesia** (*defined as decreased sensitivity to stimulation*) is reportedly higher in patients with OA, but has only been demonstrated locally (Hendiani et al., 2003; Kavchak et al., 2012).

The scientific basis for these psychophysical phenotypes are based on animal model studies, and future research is needed to confirm the proposed mechanisms for these modalities in human models. Future research should also focus on longitudinal studies with a large cohort of patients, to justify the prognostic and evaluative properties of different sensory modalities. In addition, since QST is not used consistently, there is a need for a uniformity in practice and for clinical decision rules to aid clinicians (Uddin & MacDermid, 2016).

1.5.2. Imaging phenotypes

1.5.2.1. Structural knee abnormalities

Ultrasound (US) and functional Magnetic Resonance Imaging (fMRI) techniques allow for visualization of structural damage and peripheral mechanisms linked to knee pain within the osteoarthritic knee. Features identifiable using imaging techniques within the knee are indicative of peripheral mechanisms, and are discussed extensively in Chapter 1.3.1.

1.5.2.2. Activation of regions within the CNS

MRI and other imaging techniques (e.g. Fluorodeoxyglucose positron emission tomography, FDG-PET) are not limited to the affected knee but can also be employed to changes within supraspinal regions which are indicative of central mechanisms. Knee pain has been shown to significantly activate the pain matrix (see Chapter 1.2.1.2), especially in the cingulate cortex, the thalamus, the amygdala; as well as areas involved in the processing of fear, emotions and aversive conditioning (Quante, Hille, Schofer, Lorenz, & Hauck, 2008). While some of these brain regions are activated during typical pain processing, areas such as the amygdalae have been implicated as markers of central mechanisms which augment already ongoing processing of pain processes within higher pain processing centers (Cottam, Condon, Alshuft, Reckziegel, & Auer, 2016). It is important to consider that evidence is scarce to support the use of these phenotypes in differentiating between peripheral and central pain mechanisms, and studies which implicate brain regions typically employ small sample sizes.

Distortion of the balance between inhibitory and facilitating descending modulatory systems and influences on knee OA pain have been suggested as means by which pain is enhanced in individuals with knee OA pain (Gwilym et al., 2009; Schaible, 2007). One fMRI study showed that increased activation of the RVM is specifically related to development and maintenance of CS in a chronic pain sample (Lee, Zambreanu, Menon, & Tracey, 2008).

Some studies have demonstrated relationships between imaging and QST markers of central mechanisms have also been suggested within the literature (Kulkarni et al., 2007; Staud, Robinson, & Price, 2007). For example, one fMRI study in chronic pain populations reported enhanced dorsal horn activity following TS, compared to normal controls (Bosma et al., 2016). These imaging studies, as well as associations between psychophysical and imaging markers of CS provide rationale for the role of specific brain regions in relation to knee OA pain. However, other studies have demonstrated activation of the same neural networks following social rejection (Eisenberg & Spinrad, 2004) and empathy for pain (Singer et al., 2004). While this highlights the lack of specificity of these areas constituting sole pain processing, it provides support for the multidimensional nature of pain. Moreover, evidence supporting clinical

utilisation of phenotypes identified from brain imaging approaches is lacking. There is need for clinically relevant information to define increased activation or reduced gray matter volume within relevant brain regions. Future work is needed to confirm the role of these brain regions in modulating knee OA pain, and to perhaps, provide an atlas which will aid clinicians make decisions on whether or not augmentation of central processes are present within an individual.

1.5.3. Self-report phenotypes

Knee pain is complex and may be influenced by factors not unique to the index knee joint. Large studies on individuals reporting knee OA pain have identified that around 10% individuals express greater psychological distress (Cruz-Almeida et al., 2013; Kittelson et al., 2016; Knoop et al., 2011). A recent systematic review found that self-report traits, including psychological distress, were identified across individuals reporting knee OA pain (Deveza et al., 2017).The theory behind these psychosocial constructs described here are discussed in previous chapters (See Chapter 1.2.2).

Associations between psychological- (*including anxiety, catastrophizing, depression*) and somatic- (*including sleep and pain distribution*) self-report traits and QST measures of CS have previously been demonstrated in individuals with knee OA pain (Brown et al., 2016; Campbell et al., 2015; Harden et al., 2003; Lluch et al., 2017; Lluch Girbes et al., 2016; Riddle, Wade, Jiranek, & Kong, 2010).

Imaging studies in chronic pain patients have shown associations between psychosocial factors, such as depression and cognitive impact, and changes in brain regions (Giesecke et al., 2005; Glass et al., 2011). Such evidence provides a neural basis for the effect of psychosocial factors, on chronic pain. Previous knee OA pain studies have demonstrated associations between more objective measures of CS (*including psychophysical and imaging markers*) and self-report traits, including: sleep disturbance (Finan et al., 2013; Lluch, Torres, Nijs, & Van Oosterwijck, 2014), catastrophizing (Cohen & Lee, 2015; Gwilym et al., 2009), depression (Cohen & Lee, 2015; Gwilym et al., 2009), negative affect (Cohen & Lee, 2015), anger (Cohen & Lee, 2015), anxiety (Burston et al., 2019), widespread pain distribution (Lluch et al., 2017; Lluch et al., 2014; Lluch Girbes et al., 2016), cognitive difficulties (Lluch et al.,

2017; Lluch et al., 2014) and neuropathic-like pain symptoms (Gwilym et al., 2009; Hochman et al., 2013; Moreton et al., 2015).

These self-report traits are typically measured by validated questionnaires, however, none of the existing questionnaires have been validated as measures of central mechanisms in chronic pain conditions. In addition, each questionnaire exclusively assesses an individual trait, and within clinical settings, assessing each of these self-report traits is time-consuming. One group has previously shown in a cancer population, that it is possible to assess each of these self-report traits by using single item measures (Turon et al., 2019). Addressing each of these traits, using a single item measure may support inclusion of these traits within one comprehensive questionnaire.

It is also likely that these self-report traits highlighted here are interrelated and not totally independent of each other in many chronic pain conditions (Maly, Costigan, & Olney, 2006; Scopaz, Piva, Wisniewski, & Fitzgerald, 2009). This suggests that including each of these traits within a questionnaire could allow identification of an underlying trait which associates with more objective markers of underlying pain mechanisms.

The magnitude by which changes in these traits predict changes in pain levels across individuals with knee OA pain is still contested within the literature (Gerrits, van Marwijk, van Oppen, van der Horst, & Penninx, 2015; Jensen, Turner, & Romano, 2001). Many of these self-report traits have been shown to predict poor response to peripherally acting treatment, further supporting their role as markers of central mechanisms in individuals with knee pain (Cremeans-Smith, Millington, Sledjeski, Greene, & Delahanty, 2006; Dave et al., 2017; Hodges et al., 2016; Pinto, McIntyre, Ferrero, Almeida, & Araújo-Soares, 2013; Roth, Tripp, Harrison, Sullivan, & Carson, 2007; Wylde et al., 2018; Wylde et al., 2015).

1.5.4. Summary

While OA is generally considered a peripherally mediated pain state, a subset of individuals with knee OA pain do not report pain relief after peripherally targeted treatment (Beswick, Wylde, Gooberman-Hill, Blom, & Dieppe, 2012). Such data suggests that pain associated with knee OA is a mixed state, and in

some individuals, CNS factors may play an even more prominent role in augmenting the pain experience. Thus, this “mixed” pain state seen in OA requires a more tailored approach to treatment.

By carefully assembling information from the individual, clinicians may be able to identify the subgroups of individuals based on considerations of characteristics that may be related to purely peripheral pain mechanisms, or that may include augmented central pain mechanisms. There is support within the literature for the application of the traits discussed above, as indicators of the complex mechanisms which drive pain in knee OA (Dell’Isola et al., 2016). A summary of these traits that characterize the presence of underlying pain mechanisms, and the respective measurement approaches are summarized in Table 1-3.

1.6. Stratified treatment for knee OA pain

Clinical approach to treatment is traditionally based on a ‘stepped’, ‘all-comers’ or ‘adaptive’ model of care, where treatment depends on the patient’s actual response to previously offered treatment. In comparison to the ‘all-comers’ approach, a stratified approach to treatment employs baseline information about a patient’s likely response to treatment, to formulate alternative, more efficacious treatment decisions (Padmanabhan, 2014).

Stratified medicine seeks to identify those who will have the most clinical benefit or least harm from a specific treatment (Hingorani et al., 2013). The heterogeneity seen in this prevalent condition, the clear variation in treatment responses, and the resource-intensive nature of treatments, makes a stratified approach particularly suited for the treatment of knee OA pain. Stratification can be made possible based on patient risk information, and/or underlying mechanisms, and/or prediction of treatment responsiveness (Foster, Hill, O'Sullivan, & Hancock, 2013). While the risk- and mechanisms- based approaches which employs patient risk or mechanism characteristics to identify the best possible treatment, the treatment responsiveness approach starts with an individual’s response to treatment in order to match patients to treatment.

20% to 40% of individuals with OA show unsatisfactory pain relief following treatment targeted towards the affected knee (peripherally), or towards the

central nervous system (Baker, van der Meulen, Lewsey, & Gregg, 2007; Wylde, Beswick, Dennis, & Gooberman-Hill, 2017; Wylde, Hewlett, Learmonth, & Dieppe, 2011). These results suggests that addressing distinct pain mechanisms is of great importance for optimized treatment and prognosis of knee OA pain (Malfait & Miller, 2016).

Stratification approaches have shown to be reliable and valid in a low back pain population (Hill et al., 2008; Hill et al., 2011), but are however scarce within the knee OA pain population. Previously existing self-report approaches in other chronic pain conditions such as the STarT Back (Butera, Lentz, Beneciuk, & George, 2016) and the Central Sensitization Inventory (Nishigami et al., 2018), originally designed for respective use within the back pain and central sensitivity syndrome populations, have been adapted for use within the knee pain population. These questionnaires however assume generalisability of traits across musculoskeletal conditions, an assumption which is contested within the literature. For example, characteristics such as pain-related fear of movement (kinesiophobia) and self-efficacy included within the STarT Back tool have been shown to be important in predicting back pain (Alhowimel, AlOtaibi, Radford, & Coulson, 2018; Roberts, Dew, Bridger, Etherington, & Kilminster, 2015), but not knee OA pain (Gunn et al., 2017; Somers et al., 2009; Tichonova, Rimdeikienė, Petruševičienė, & Lendraitienė, 2016; Wylde, Dixon, & Blom, 2012a). The self-report tool proposed for development in this thesis will seek to include items linked to both peripheral and central mechanisms.

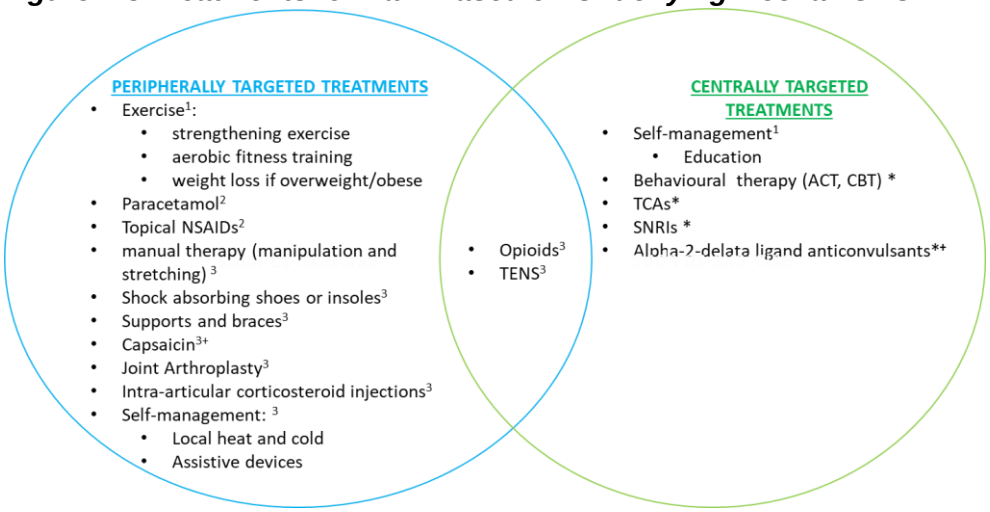
In addition, other characteristics such as neuropathic-like pain symptoms that are relevant to the knee OA pain population (as discussed in Chapter 1.5.3) are not accounted for within either the STarT Back (Butera et al., 2016) and the Central Sensitization Inventory (Nishigami et al., 2018). These findings together supports the need for a mechanism-based stratification tool which includes characteristics relevant to the knee pain population.

Such a tool is particularly aimed towards supporting primary/first-contact care decision making, in secondary care and other community settings. Knowledge concerning patient characteristics (*phenotypes*) related to underlying mechanisms could help clinicians direct limited resources to those most likely to benefit from specific mechanism-based treatment.

Identifying the presence of either peripheral and/or central mechanisms across individuals with knee OA could 'fast track' towards an appropriate course of treatment, whilst steering individuals away from non-beneficial investigation and treatment.

Figure 1-3 illustrates the various mechanisms through which existing treatments are suggested to act. However, for many of these treatments, no definitive studies have been conducted to confirm the exact pain mechanisms through which these compounds or interventions would primarily benefit knee OA pain relief. Generating a mechanism-based stratification tool specific for use within the knee pain population will inform future RCTS which may seek to highlight what specific treatments are useful based on underlying mechanisms.

Figure 1-3 Treatments for Pain Based on Underlying Mechanisms.



*Treatments not recommended by NICE due to lacking or conflicting evidence on efficacy and/or safety are still unavailable.
+Antineuropathic agents.
1=Core treatment recommendation according to NICE.
2=Second line of treatment recommendation according to NICE.
3=Third line of treatment recommendation according to NICE.
Anti-TNF (Anti- Tumour Necrosis Factor); DMARDS (Disease Modifying AntiRheumatic Drugs); NSAIDs (Non-Steroidal Anti-Inflammatory Drugs); TKR (Total Knee Replacement); TENS (Transcutaneous Electrical Nerve Stimulation); CBT (Cognitive Behavioural Therapy); ACT (Acceptance and Commitment Therapy); SNRIs (Serotonin- and Norepinephrine- Reuptake Inhibitors); TCAs (Tricyclic Antidepressants).

There are varying extents for data collection using a subgrouping tool in the clinic or outside of the clinic. If data are collected in the clinic, patients need private space to complete the tool. Data collection outside the clinic does not

require space in the clinic for questionnaire completion but does require personnel to manage the process and, for nonautomated options, data entry. Computers (including smart phones and handheld devices) are likely to be more commonly used for data collection in the future, given their increasing prevalence and many advantages, including directly integrating the questionnaire data in the electronic medical record and prompting automated alerts to clinicians. In paper-based clinics, questionnaire results would be expected in hard copy. In clinics using electronic systems, questionnaire results need to be integrated within the electronic medical record system, either by collecting the data electronically and linking them or adding nonelectronic results to the electronic data.

Significant impact of treatment stratification has been demonstrated within the back pain population with one group reporting a mean increase in quality-adjusted life years (QALYs) and cost savings, compared to current best standard of care for low back pain (Hill et al., 2011). Similar successes have been reported in other medical fields, for example, breast cancer (Ginsburg & Willard, 2009; Padmanabhan, 2014).Thus, development of a self-report stratification tool has potential to have significant impact on patient outcomes, clinical behaviour, resource use and costs.

1.7. Scope of the Project

Significant advances in our understanding of pain mechanisms are finally making the vision of “personalised analgesia” seem within our grasp. Stratification between knee OA pain phenotypes linked to underlying mechanisms could inform distinct mechanism-based therapeutic approaches that could be tailored to specific subsets of patients.

In people with knee OA pain, mechanism-based subgrouping using imaging, QST or self-report approaches may allow individuals to allow benefit from treatment targeted towards those underlying mechanisms. While imaging techniques pose the most objective modality, they are also the most expensive in comparison to QST or self-report approaches. Use of imaging techniques contributes to a dramatic rise in healthcare costs associated with imaging, and some have argued that the costs associated with imaging are out of proportion to any possible benefit. One group in the United States reported a 12% increase in imaging expenditure for the CNS and spine has

previously been reported in the United States (Smith-Bindman, Miglioretti, & Larson, 2008). In the midst of rising healthcare costs however, cost effective, feasible and sustainable means of identifying mechanistic subgroups within individuals with knee OA pain are warranted.

There is emerging evidence that suggests a role of psychophysical traits in identification of pain mechanisms, as measured using QST approaches. However, the evidence to direct the diagnostic or therapeutic prediction rules of this approach in knee OA pain is lacking. Lack of normative values, and lack of standardized methods are some key hindrances in the use of QST approaches for mechanism based subgrouping. There is need to continue testing to develop reliable and clinically feasible QST protocols that require less time and inexpensive portable equipment.

While self-report (questionnaire) approaches show less objectivity compared to QST and imaging, equipment for the latter are costly and the techniques are time consuming. Thus, the current project intends to adopt concepts of stratification employed within the back pain literature (Hill et al., 2008), by attempting to identify underlying knee OA pain mechanisms using a self-report tool. This could provide an alternative approach for stratifying patients reporting knee OA pain, with the ultimate aim of effective mechanism-based subgrouping within such a heterogeneous population. Successful development of a self-report measure which identifies underlying pain mechanisms may subsequently improve therapeutic response, and subsequently improving the current economic impact of knee OA.

1.8. Hypothesis

This project hypothesizes that a concise and validated set of self-report questions, representative of traits associated with peripheral and/or central pain mechanisms, can identify mechanism-based subgroups across individuals reporting OA knee pain.

1.9. Aims and Objectives

1.9.1. Aims

Overall, this PhD project sought to develop a valid and concise self-report questionnaire with items representative of traits shown to be associated with peripheral and/or central OA knee pain mechanisms.

1.9.2. Objectives

The key objectives of the PhD project were:

1. To identify and select questionnaire items which most represent traits shown to be associated with measures of peripherally driven or centrally augmented knee OA pain, using questionnaire and clinical data from a community knee pain population.

2. To determine the predictive validity for traits selected for inclusion within the developing questionnaire, using psychophysiological and questionnaire assessments in individuals with chronic knee pain.

3. To explore interpretation of the standardized questions intended for inclusion within the newly developed questionnaire using interview approaches, and to determine the psychometric properties of the questionnaire across a knee pain population.

2. METHODS

2.1. Summary

There are many steps to questionnaire development. Initially, items are generated and their content validity is assessed. The questionnaire is then constructed by pre-testing the selected questions, administering the survey, reducing the number of items, and understanding how many underlying traits (*also referred to as factors*) the questionnaire captures. Finally, questionnaire evaluation assesses the reliability and validity of the final questionnaire is assessed (Boateng, Neilands, Frongillo, Melgar-Quiñonez, & Young, 2018). Some of the steps align with the methods employed in the development of other valid, and reliable tools, such as the StartBack (Hill et al., 2008). These steps will therefore guide questionnaire development described throughout this thesis.

Table 2-1 below outlines each major study which contributes data that addresses the project objectives (Chapter 1.9). This chapter provides background details of the KPIC study which contributes data to the first three results chapters of this thesis. A statement of ethical approval and informed consent prior to the onset of each study, recruitment details and assessments conducted on participants are described.

The chapter further describes the quantitative analytic procedures employed throughout the project, and closes by providing a signpost for the content of subsequent result chapters to follow.

Table 2-1. Details of studies employed across thesis result chapters.

Results Chapter	Study Sample	Aims	Time points
Item generation: self-report traits associated with peripheral and central pain mechanisms. [a]	KPIC cohort study	To generate a shortlist of self-report questions which reflect traits associated with underlying pain mechanisms	Baseline
Item selection: self-report traits associated with a QST **measure of central pain mechanisms.** [a]	KPIC cohort study	To select a valid set of self-report questions that measure a phenotypic trait associated with central pain augmentation	Baseline
Predictive validity: baseline self-report 'central mechanisms' trait as a predictor of persistent knee pain.	KPIC cohort study	To investigate the ability of the selected self-report questions which measure 'central mechanisms' to predict 1-year pain outcomes	Baseline Year-1 follow-up
The Central Aspects of Pain in the Knee (CAP-Knee) questionnaire: standardization and development.	The CAP-Knee questionnaire: Question Evaluation and reliability study	To understand participants' interpretation of questions included within the CAP-Knee questionnaire.	Baseline
The CAP-Knee questionnaire: a psychometric evaluation. [a]	Investigating musculoskeletal health and wellbeing' study	To evaluate the psychometric properties of the CAP-Knee questionnaire.	Baseline Time 1 follow-up

[a]Chapters describe secondary analyses of previously existing dataset.

2.2. Knee Pain and Related Health in the Community (KPIC) study cohort study

2.2.1. Outline

Secondary analyses of data collected by the Knee Pain and Related Health in the Community (KPIC) study team (Fernandes et al., 2017) allowed access to a large item pool (items = 104), and large sample population of individuals with knee pain (n=2152), some of whom had also undergone further clinical assessment (n=322). The KPIC study began baseline recruitment in 2014, with baseline recruitment scheduled to end by 2015. Subsequently, year 1 recruitment began in 2015 and ended in 2016.

Within the context of this project, data from the KPIC cohort study informed generation, selection and validation of items included within the developing self-report tool.

2.2.2. Ethics

The KPIC study protocol was approved by the Nottingham Research Ethics Committee 1 (NREC Ref: 14/EM/0015) and registered (clinicaltrials.gov portal: NCT02098070).

2.2.3. Study design

The KPIC study is a cohort study of community dwelling adults within the Nottinghamshire and Derbyshire community, which employed a cluster sample procedure (with General Practice, GP, acting as the cluster).

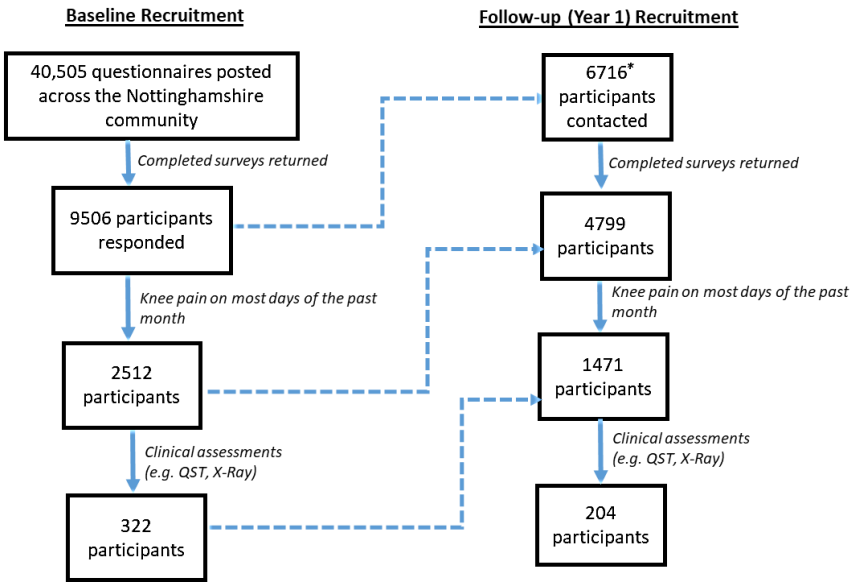
2.2.4. Participants and Recruitment

KPIC participants were recruited across 12 GPs in the Nottinghamshire and Derbyshire community. Regional GPs were approached via the Clinical Research Network (East Midlands), including Nottinghamshire and Derbyshire. All men and women aged 40 years old or over, located on the GP register, irrespective of knee pain status were eligible for inclusion in the study. Exclusion criteria for participants were: known terminal illnesses, severe psychiatric illness and dementia, or any other conditions or circumstances that make them unstable to receive a questionnaire. Eligibility was decided by health professionals in each GP, using the GP register.

At baseline and follow-up time points, postal questionnaires sent to participants were accompanied by a covering letter from their GP introducing the study aims and objectives, an enclosed pre-paid envelope to Academic Rheumatology (University of Nottingham) at Nottingham City Hospital. At the end of each postal questionnaire, participants were asked to indicate whether or not they would be willing to: (i) receive further information about a single visit to Academic Rheumatology to undergo knee radiographs and other assessments; (ii) receive further similar postal questionnaires in one year's time; and (iii) receive further information of other future studies related to knee pain and knee OA (Fernandes et al., 2017).

The proportion of individuals recruited over baseline and year-1 follow up time points are illustrated in Figure 2-1 below.

Figure 2-1. KPIC Recruitment Flowchart.



* These participants consented to further contact

2.2.5. KPIC survey design

The KPIC baseline survey (Appendix 1, p250) was designed to capture detailed information about the individual, their medical history and currently known risk factors for knee pain and knee OA (Fernandes et al., 2017). Participants were asked about the presence and history of knee pain. A validated 'yes' or 'no' screening question was used to determine the presence

of current knee pain, specifically: “Have you had knee pain for most days of the past one month?” (Reilly, Muir, & Doherty, 1996; Thomas et al., 2002).

Knee pain experience and patterns was captured using the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire (Hawker et al., 2008). Participants were also asked to rate their current knee pain severity using a numerical rating scale (NRS) from 0–10, where ‘0’ is no pain at all and ‘10’ is worst imaginable pain.

Survey and clinical assessment data from participants reporting knee pain on most days of the past month either at (i) baseline or (ii) at baseline and year 1 follow up, were assessed in this project.

Several psychological and somatic traits linked to knee OA pain and underlying mechanisms were assessed within the KPIC survey. Pain distribution was captured using a body pain manikin (Lacey, Lewis, Jordan, Jinks, & Sim, 2005). The manikin was coded according to 45 discrete sites (Appendix 2.1, *p273*). The Pain Catastrophizing Scale (PCS) was used to determine whether participants had an exaggerated negative orientation towards a noxious stimulus (Sullivan, Bishop, & Pivik, 1995). Anxiety and depression symptoms were measured using the Hospital and Anxiety Depression Score (HADS) which has been extensively validated (Zigmond & Snaith, 1983). The 12-item Short Form Survey (SF-12) measured constructs of physical and mental function (Ware, Kosinski, & Keller, 1996) was also included within the KPIC survey. The effect of symptoms subscale of the Illness Attitude Scale (Ferguson & Daniel, 1995), measured the extent to which symptoms interfere with normal daily activities. A set of items from the Medical Outcomes Survey (MOS)-sleep scale were also employed to record dimensions of sleep, including sleep adequacy and somnolence (Hays, Martin, Sesti, & Spritzer, 2005).

The KPIC survey at year 1 (Appendix 3, *p278*) followed a similar format to the baseline survey, and contained questions included within the KPIC baseline survey.

2.2.6. KPIC clinical assessment

From the questionnaire responders, a sample of participants who indicated willingness to consider undergoing knee radiographs and other assessments were identified.

To examine how knee pain and associated factors change over time, the KPIC study recruited three distinct groups of participants (early knee pain, established knee pain and no knee pain) based on their questionnaire responses on knee pain duration and severity. These individuals underwent an additional telephone screening process prior to being booked into a single appointment within the department (Academic Rheumatology, University Of Nottingham).

The inclusion criteria for clinical assessment at baseline were:

i. Participants with recent-onset knee pain (n=219) were defined as mild/moderate and/or intermittent knee pain occurring for the first time in the past 3 years for most days of at least one month, unrelated to obvious major trauma;

ii. Participants with established persistent knee pain (n=103): defined as knee pain for over 3 years which has been moderate or severe (NRS >6) and/or persistent for most days of the past 3 months, unrelated to obvious major trauma;

iii. Participants with no knee pain: defined as no knee pain (n=98) within the past 5 years.

Clinical assessment data employed within this thesis were restricted to radiographic and PPT assessments across individuals with knee pain at baseline.

2.2.6.1. Baseline Pressure pain detection threshold (PPT) assessment

PPT is defined as the minimum force required to induce pain (Maquet, Croisier, Demoulin, & Crielaard, 2004). As discussed in Chapter 1.5.1.1, psychophysical measures, such as PPTs, can act as mechanism-based classification indices and compare responses within participants (e.g. affected

vs. unaffected sides) and across multiple body regions between individuals (Arendt-Nielsen et al., 2010; Graven-Nielsen & Arendt-Nielsen, 2010).

In the KPIC cohort, assessments for each participant were undertaken using a standardized protocol by 1 of 2 trained researchers (Fernandes et al., 2017). PPT was measured using a hand-held pressure algometer with a circular (1 cm^2) padded-tip probe connected to a computer with outputs analysed by dedicated software (Somedic AB, Sweden). Pressure was applied with a standardised 30 kPa/s ramp until the participant indicated, by pressing a button, a change from pressure to pain sensation. Participants were familiarised with the PPT procedure twice on fingernails of the non-dominant hand. Each PPT testing cycle was conducted at the sternum (3-cm caudal to the sternal notch), the medial and lateral tibiofemoral joint lines adjacent to the patellar ligament of each knee, and the proximal tibia (5-cm distal to the tibial tuberosity of each leg). The PPT cycle was repeated 3 times with a 2-minute rest period between each cycle. PPT values (kPA) for each site were averaged across the 3 cycles.

Intra-rater and inter-rater agreements for PPT scores used in this study have been published (Akin-Akinyosoye et al., 2018), and concordance correlation coefficients (CCC) were good (Intra-rater CCC range = 0.51 to 0.86; Inter-rater CCC range = 0.39 to 0.90).

2.2.6.2. Baseline KPIC radiographic assessment

Bilateral weight-bearing semi-flexed posterior-anterior tibio-femoral views using a Rosenberg template, and 300 flexion skyline patello-femoral views were undertaken using standardised protocols. All radiographs for this study were obtained in Picture Archiving and Communication System (PACS) electronic format and analysed using the Hipax Digital Imaging and Communications in Medicine (DICOM) software. The weight-bearing semi-flexed posterior-anterior view has been shown to have better sensitivity to define JSN (Duncan et al., 2015), and therefore is recommended by OARSI for evaluating tibio-femoral OA (Hunter et al., 2015). The skyline view is preferred to the lateral patello-femoral view since it provides a clearer view of joint space width and permits determination of medial versus lateral narrowing in the patello-femoral joint (Hunter et al., 2015).

Grading of radiographs for OA within each knee compartment employed the use of ***K&L scoring*** (Kellgren & Lawrence, 1957), which focuses on characteristics within the affected knee, including osteophyte formation, joint-space narrowing (JSN) and bone sclerosis, and provides simple and practical ordinal scales for each characteristic. The KL classification combines osteophyte presence and JSN scores, creating a composite score ranging from 0 (No features of OA) to 4 (Greatly reduced joint space, and subchondral sclerosis) – Chapter 1.3.1., Table 1-1.

In this project, the extent of radiographic damage was primarily accounted for using tibiofemoral KL scores (Hunter et al., 2015). ***Presence of ROA*** was defined as definite JSN (grade 2) plus definite osteophyte (grade 2) in any compartment (tibiofemoral or patellofemoral). This definition of definite osteophyte and definite narrowing is consistent with the pathological definition of OA which requires both definite focal loss of hyaline cartilage and definite associated bone change (Braun & Gold, 2012).

Intra- and inter-rater agreements for radiographic scoring used in this project have previously been published (Akin-Akinyosoye et al., 2019), and were shown to have substantial agreement (Intra-rater weighted kappa range = 0.66 to 0.90; Inter-rater weighted kappa range = 0.65 to 0.93).

2.2.7. KPIC Data management

Each participant was allocated a unique study identifier number at baseline, which was linked to follow-up reports by the same participant, where available. All data were entered directly into a pre-prepared form within Microsoft Access 2007 database constructed by the database manager for the KPIC study. The data entered were limited to the possible range for each variable to minimise erroneous scoring, with any missing observations coded as ‘999’ for all variables. The paper questionnaires and clinical assessment data were appropriately catalogued and stored within the Department of Academic Rheumatology.

2.3. Quantitative analyses

2.3.1. Descriptive analysis and Basic statistics

Assumption of normality was assessed for all continuous variables used within this project, by employing visual inspection of histograms and the Shapiro-Wilks test (Armitage, Berry, & Matthews, 2008; Royston, 1992).

Mean and Standard Deviation (SD) values were presented for normally distributed variables, meanwhile, median and inter quartile ranges (IQRs) were presented for non-normally distributed, or categorical variables.

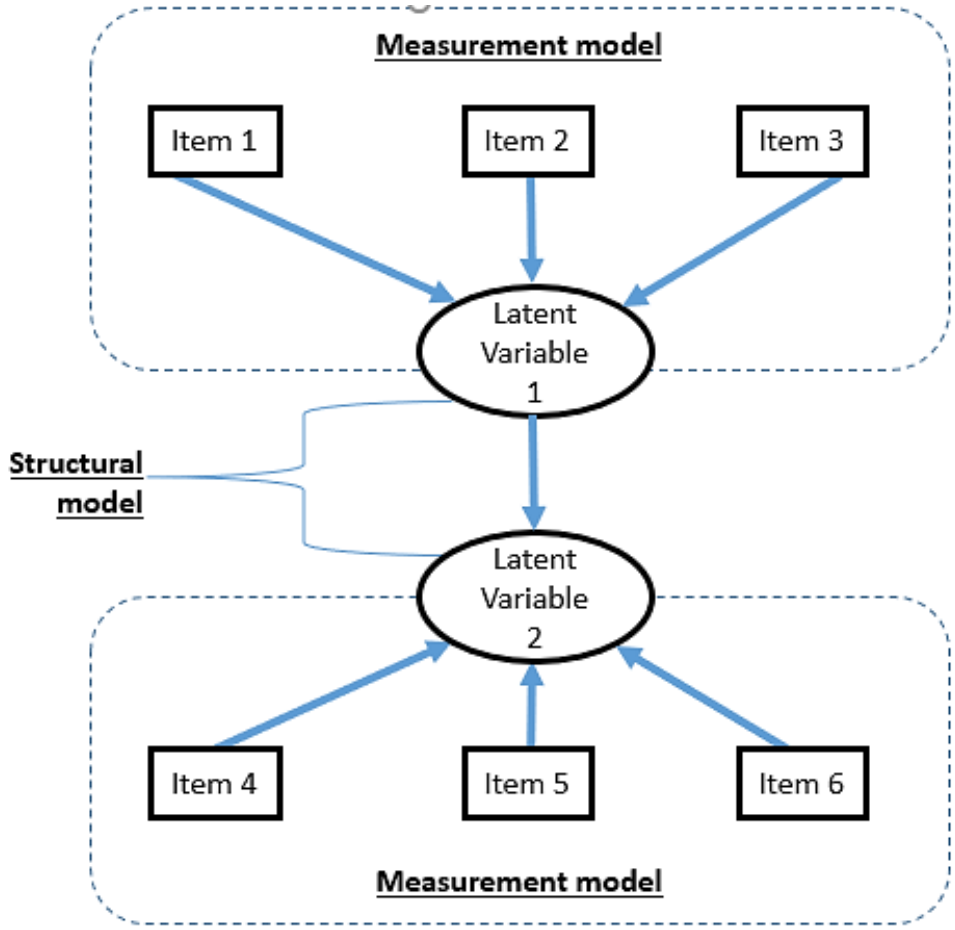
Parametric assessments (e.g. linear regression models) were employed for assessment of normally distributed data, while non-parametric tests (e.g. Spearman's rank correlation coefficient or logistic regression models) were employed during assessment of non-normally distributed data (Armitage et al., 2008).

Chi square (X^2) tests were used to compare categorical variables (e.g. difference in proportions on individuals with or without pain distribution), while a two sample t-test for independent groups compared normally distributed continuous data obtained from two independent groups (e.g. mean age between men and women) (Armitage et al., 2008). A paired t-test was used to compare normally-distributed continuous data from a dependent group (e.g. test score compared between baseline and follow-up) (Armitage et al., 2008).

2.3.2. Structural Equation Modelling (SEM)

SEM uses multivariate regression to relate patterns of responses (e.g. questionnaire responses) to a set of latent factors (also referred to as a 'latent variable', or 'latent trait', or 'latent construct) (Bentler, 2007; Moreno, de Luna, Gómez, & López, 2014).SEM in this project was based on the assumption that the structural model (relationship between the latent variables) is nested within the measurement model (the part of the model that examines relationship between the latent variables and their observed measures) – Figure 2-2 (Anderson & Gerbing, 1988).

Figure 2-2. Difference between a measurement model and a structural model.



The Structural model describes the relationship between the latent variables.
The measurement model describes the relationship between the latent variables and their indicators.
The measurement model portrayed here is also representative of a confirmatory factor analysis (CFA) model.

2.3.2.1. Determination of model fit

The goal of SEM is typically to find a practical model based on substantive theory, which fits statistically with the data well. Absolute fit indices are a group of indices that indicate how well the model fits in comparison to no model at all. Fit indices included in this category include the Chi-Squared (X^2) test, root mean square error of approximation (RMSEA) for continuous data, and the weighted root mean residual (WRMR) for categorical data (Hooper, Coughlan, & Mullen, 2008).Incremental fit indices on the other hand, compare the X^2 to a baseline model, testing the hypothesis that all variables are uncorrelated (McDonald & Ho, 2002). Fit indices included in this category include the Comparative Fit Index (CFI), and the Tucker Lewis Index (TLI).

For acceptable threshold levels of fit, in the current project, the model fit was determined by a CFI and TLI at values greater than 0.96, RMSEA < 0.05, and WRMR < 1 (Hooper et al., 2008). Difference testing compared the nested model to the overall model to demonstrate whether or not significant ($p<0.05$) changes to the model fit existed where relevant.Weighted Least-Squares Means and Variance (WLSMV) estimation algorithm was employed due to the categorical nature questionnaire items assessed within this project. WLSMV uses polychoric correlations (i.e. correlation when the data consists of two ordinal variables, such as Likert-type survey data), and relies on adjustments to the X^2 test statistic to accurately create parameter estimates, and test statistics depending on the data and model conditions (Rhemtulla, Brosseau-Liard, & Savalei, 2012).

2.3.2.2. Factor analytic procedures within the SEM framework

The interest in validity within this project is to determine how well a questionnaire measures what it is purported to measure. This is commonly referred to as 'construct' or 'factorial' validity. To establish construct validity a measurement model is needed. Exploratory Factor Analysis (EFA) within the SEM framework (also referred to as Exploratory SEM, ESEM), and confirmatory factor analysis (CFA) gives access to all the usual SEM parameters, such as fit indices, in order to determine construct validity of a measure. Unlike EFA/ESEM which is largely data driven and exploratory in nature, CFA requires explicit specification of every aspect of the evaluated model. Thus, a strong conceptual or empirical foundation is needed to guide specification and evaluation of CFA models.

During questionnaire construction, the standard progression is for researchers to begin by specifying an exploratory model to evaluate an initial pool of items, and to then move to a confirmatory model to provide a more rigorous evaluation of how a theoretical measurement model represents the observed data. Through this process, researchers are able to determine the number of latent variables that best represents the latent trait of interest, and the pattern or strengths of relationships (i.e. factor loadings) between the observed items and latent variables (Gallagher & Brown, 2013). Item loading scores represent the regression coefficient between an item and the identified factor (Salkind, 2010).

Analyses employing the SEM approach were conducted using MPlus version 7.4 (Muthén, 2012).

2.3.3. Inter-rater reliability (IRR)

Well-designed studies seek to demonstrate consistency among observational ratings provided by multiple coders: IRR. IRR can be analysed using Cohen's kappa statistic (κ) or weighted kappa (κ_w) for categorical variables (Cohen, 1960), or Intraclass Correlation Coefficient (ICC) for interval and ratio variables (Mandrekar, 2011)..

2.3.3.1. Cohen's kappa

Similar to correlation coefficients, Cohen's kappa statistic (κ) can range from −1 to +1, where 0 represents the amount of agreement that can be expected from random chance, and 1 represents perfect agreement between the raters.

Unlike correlation approaches, Cohen's kappa accounts for agreement between the two or more raters, but not the degree of agreement, which is especially relevant when the ratings are ordered. To address this, the weighted kappa (κ_w) statistic uses a predefined table of weights which places weights that account for degrees of agreement between the ranked categories. In this project, the importance of agreements in measuring different categories of a variable was equal, thus, weights were assigned equally (Armitage et al., 2008).

Different authors (Cicchetti & Sparrow, 1981; Fleiss, 1981; Landis & Koch, 1977)have proposed various criteria for the magnitude of kappa and weighted kappa, summarized in in Table 2-2. While they differ with regard to terminology and exact cut-off values, they together support the notion that values less than 0.6 are not useful, and values ≥ 0.75 are desirable. Throughout this thesis, the Landis and Koch approach was implemented. Kappa and 95% CI were reported (Reichenheim, 2004).

Values of only 0.50 to 0.60 suggests that less than 50% of the data being analysed are erroneous, and the confidence intervals about the obtained kappa are sufficiently wide that one can surmise that about half the data may be incorrect (Simundic, 2008). In such cases, statistical significance should

therefore be interpreted with caution when so much error exists in the results being tested.

Table 2-2. Interpretation of Cohen's kappa

Value of Kappa	Landis and Koch	Cicchetti and Sparrow	Fleiss	% of reliable data
≤0.20	Poor to slight	Poor	Poor	0–4%
0.21 to 0.39	Fair			4–15%
0.40 to 0.59	Weak	Fair	Fair to good	15–35%
0.60 to 0.75	Moderate	Excellent		35–63%
0.75 to 1.00	Strong to Almost Perfect		Excellent	64–100%

2.3.3.1. Intra-class Correlation Coefficient (ICC)

In this project, ICC was employed to assess agreement between the absolute values of the developing tool across two time points - test retest reliability (or repeatability).

Unlike other agreement approaches which are based solely on agreement (such as the paired *t* test and Bland-Altman plot), or on correlations (such as Pearson correlation coefficient), the ICC reflects the degree of both correlation and agreement between numerical or continuous measurements (Koo & Li, 2016). This approach, also referred to as ICC(2,1) or ICC(A,1), models an effect of the individual and of the time point, when response was provided, and assumes that the study participants were drawn from a larger population. An ICC less than 0.5 indicates poor agreement, between 0.5 - 0.74 moderate agreement, between 0.75 - 0.90 good agreement and >0.90 excellent agreement (Koo & Li, 2016).

2.3.4. Establishing optimal cut-off points

Development of a classification tool, such as questionnaires, for clinical purposes requires that the developers establish diagnostic utility of the tool against a gold-standard criterion.

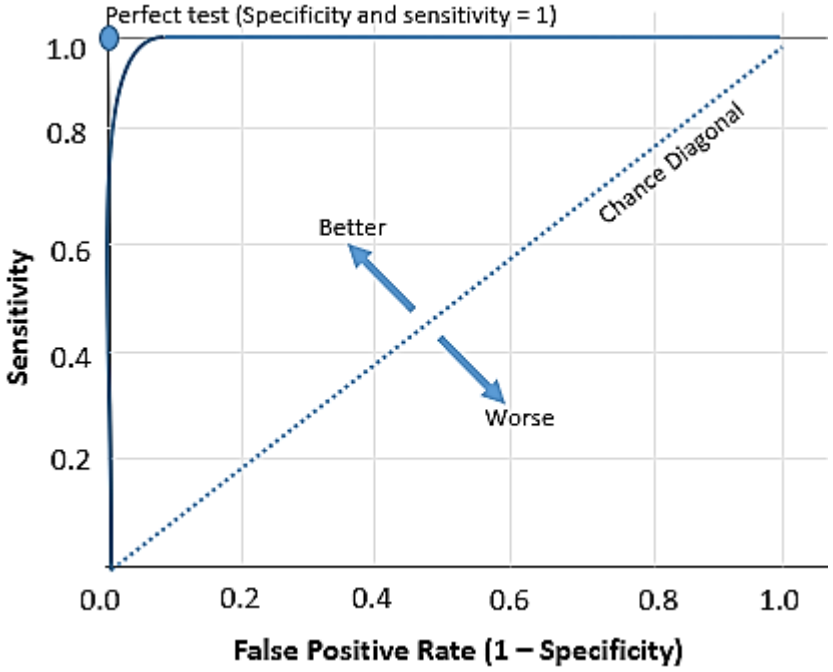
Receiver operator characteristic (ROC) analysis is used commonly in clinical epidemiology to quantify how accurately medical diagnostic tests (or systems) can discriminate between "cases" and "non-cases" (Swets, 1986, Green and Swets, 1966, Metz, 1978, Metz, 1986). Derived indices, such as the area under the ROC curve (AUC) (Hanley and McNeil, 1982, McNeil and Hanley, 1984, Wieand et al., 1989, McClish, 1989), are the most commonly used to measure diagnostic accuracy, including sensitivity and specificity in comparison with gold standard test (Swets, 1979).

- Sensitivity (“a positive case”) refers to the proportion of subjects who are indeed cases (reference standard positive) and give positive test results, also referred to as True Positive Rate (TPR) (Hajian-Tilaki, 2013).
- Specificity (“a negative case”) is the proportion of subjects who are not cases and give negative test results, also referred as True Negative Rate (TNR) (Hajian-Tilaki, 2013).

ROC curves (Figure 2-3) displays the discriminatory capacity of a test and is a plot of 1−specificity (the False Positive Rate, FPR) of a test on the *x*-axis, against its sensitivity on the *y*-axis, for all possible cut-off points. As shown in Figure 2-3, the perfect classification tool would yield a maximum AUC of 1 on the ROC curve (FPR=0, sensitivity=1) and rises steeply on the left axis of the ROC curve (Pepe, Longton, & Janes, 2009). Meanwhile an uninformative classifier would yield an AUC of 0.5 or below, which is visualized on the ROC curve as a diagonal 45 line, or a convex shaped curve lying below the diagonal line (Pepe et al., 2009).

The AUC is especially useful in a comparative study of two diagnostic tests (or systems) as they form the basic test statistics to compare ROC curves for two different classifiers. A widely used method for ROC comparisons employs bootstrapping techniques to derive a Wald chi-squared statistic in order to report a p-value (Pepe et al., 2009).

Figure 2-3. Example of a Receiver Operating Characteristic (ROC) Curve.



The 45° diagonal line shows the ROC of an uninformative test.
The blue circle is the ideal point of maximum Sensitivity and Specificity.
The False Positive Rate (FPR) defines how many incorrect positive results occurs among all negative samples available during the test.

2.3.4.1. Optimal cut-off values

Each data point on the ROC curve represents a different cut-off point with corresponding sensitivity and specificity (Pepe et al., 2009). Sensitivity and specificity vary with the cut-off chosen for a diagnostic test and ROC analysis enables the best cut-off on the diagnostic test to be assigned for clinical utility. One of the frequently used criterion for determination of the test cut-off value is the one corresponding to this particular point, where sensitivity equals specificity (Habibzadeh, Habibzadeh, & Yadollahie, 2016). If two tests are to be compared, it is desirable to compare the entire ROC curve rather than at a particular point (Swets, 1979).

2.3.4.2. Logistic regression approaches

Logistic regression models are often fitted in biomedical research in order to predict the prognosis of individual patients (Steyerberg, Eijkemans, Harrell, & Habbema, 2000). The discriminative ability of a logistic regression model is frequently assessed using the concordance (or c) statistic, a unitless index denoting the probability that a randomly selected subject who experienced the outcome will have a higher predicted probability of having the outcome occur

compared to a randomly selected subject who did not experience the event (Austin & Steyerberg, 2012). The discrimination of a logistic regression model can also be described by the AUC and evaluates the predictive performance of the diagnostic test and other variables (Zweig & Campbell, 1993). The area under the ROC curve is equivalent to the c-statistic (Hanley & McNeil, 1982).

The addition of other variables (*covariate information*) would create an improved ROC curve of the logistic model. Thus, various ROC curves could be examined to determine whether overall, addition of other variables to the logistic regression model could significantly (*or not significantly*) improve the predictive performance of the initial model which only includes the diagnostic test. This process is typically referred to as incremental validity (Hosmer Jr, Lemeshow, & Sturdivant, 2013; Seshan, Gönen, & Begg, 2013).

2.3.5. Rasch Modelling

Rasch measurement models are a family of measurement models used widely to examine and validate psychometric properties of measurement instruments (Linacre, 1994; Wright & Masters, 1982). The Rasch framework allows procedures for constructing and revising self-report questionnaires, and documenting the associated measurement properties (*e.g. reliability, construct validity*). Rasch techniques also offers questionnaire developers the opportunity to make critical corrections when using raw test scores, by allowing nonlinear raw data to be converted to a linear scale, which can then be evaluated through the use of parametric statistical tests (Boone, 2016).

Rasch analyses assesses the fit between data obtained on a questionnaire and predictions of the Rasch model, by assessing two parameter estimates: person ability (*also referred to as person logit, where a logit is a translation of the raw score*) and item difficulty (*item logit*) (Pallant & Tennant, 2007).

2.3.5.1. Rasch models

Unlike the traditional Rasch Model which is useful for dichotomous data (e.g. ‘yes’ or ‘no’ responses), analyses for this project focuses on Likert-type data, which are typically assessed using either the Rating Scale- (Andrich, 1978) or the Partial Credit- model (Masters & Wright, 1997). The Rating Scale Model is one in which all items (or group of items) share the same rating scale structure. The Partial Credit Model (PCM) can be seen as a modification of the

Rating Scale Model (RSM), where each item (or group of items) has a unique rating scale structure.

These Rasch models for polytomous items define the probability of a response in a certain category as a function of the person's ability, and item characteristics. Hence, unlike the traditional model, the rating scale- and partial credit- models describes the relationship between item difficulty and person ability, while taking threshold for the items into account (Retief, Potgieter, & Lutz, 2013). In general, for *n* response categories, there are *n*-1 thresholds, with each threshold assigned its own estimate of difficulty.

The Rasch model is driven by three main assumptions:

(i) Unidimensionality: All items forming the questionnaire measure only a single construct, i.e. the latent trait under study;

(ii) Response dependency: The response to a given item is independent from the responses to the other items in the questionnaire; and

(iii) Measurement invariance: Equivalence of item parameters across multiple populations or person ability levels.

In this project, response dependency of items was indicated where relationship between items within the residual correlation matrix was less than 0.3 (Tennant & Conaghan, 2007).Residuals are those part of the observations not explained by the Rasch dimension, and according to the Rasch model, should be random and lack structure. Thus, contrast of the residuals was conducted to test for a breach of unidimensionality (Smith Jr, 2002; Tennant & Conaghan, 2007; Tennant & Pallant, 2006). This test takes the patterning of items in the residuals, examining the correlation between items and the first residual factor, and uses these patterns to define 2 subsets of items (i.e., the positively and negatively correlated items). Identification of these 2 subset of items indicates unidimensionality supports a unidimensional rasch model (Tennant & Conaghan, 2007).

For broad assessment of measurement invariance across groups of individuals, ANOVA with a Bonferroni correction was applied to explore DIF for age and sex.

2.3.5.2. Fit statistics

Reliable summary or parameter (item and person) fit statistics play an important part in the evaluation and identification of misfit, which is critical to the development of unidimensional instruments which fit the Rasch model expectations (Smith-Bindman et al., 2008).

The **item-trait test of fit** examines the consistency of all item parameters across the person ability. Data are combined across all items to allow chi-squared assessment for item-trait interaction, in order to give an overall test of fit. A significant p-value at the 0.05 level, with a Bonferroni adjustment for the number of items, indicates a lack of consistency of item parameters across the different person abilities, thus compromising the required property of invariance (Pallant & Bailey, 2005; Pallant & Tennant, 2007). In addition, **mean and standard deviations fit residuals** are calculated for items and persons. These values are transformed to estimate a *z*-score representing standardised normal distribution and given good fit, the means should be close to 0 and the standard deviations about 1 (Pallant & Bailey, 2005; Pallant & Tennant, 2007; Shea, Tennant, & Pallant, 2009). However, values for differentiating “fit” and “misfit” are arbitrary and should be sufficiently flexible to allow for researcher judgement.

During parameter level assessment of the Rasch model, two types of mean square fit statistics, namely the **infit mean square** (*also referred to as the weighted mean square*) and **outfit mean square** (*or unweighted*) are considered. Infit is a weighted goodness-of-fit statistic, which is relatively more affected by unexpected responses closer to item and person measure (*inlier sensitive*) (Bode & Wright, 1999). Outfit is unweighted and is therefore sensitive to extreme unexpected responses (*outlier sensitive*) (Bode & Wright, 1999). Both infit and outfit statistics have an expected value of 1 and an accepted range of fit of 0.5 to 1.5 (Green & Frantom; Linacre, 2006).

Observed misfit can be categorized either as “overfit” or “underfit”. Although it provides a guide to refining an instrument, it is otherwise probably of little

concern. As a rule of thumb, under fit (“noise”) is indicated by a mean square value >1.2, and suggests unusual and/or inappropriate response patterns (Wright, 1994). Over fit is indicated by mean square values less than 1.0. Over fit is interpreted as too little variation in the response pattern, perhaps indicating the presence of redundant items (Wright, 1994).

Items demonstrating more or less variation than predicted by the model can be considered as not conforming to the unidimensionality requirement of the Rasch model. Person fit to the Rasch model is an index of whether individuals are responding to items in a consistent manner or if responses are erratic. Typically, response may be inconsistent when people are bored and inattentive to the task, or when they are confused. Similarly, an item may “misfit” because it is too complex, confusing, or because it actually measures a different construct.

2.3.5.3. Wright maps

A Wright map provides both person and item measures on the same linear scale and allows the researchers to evaluate how well the test items are measuring a variable based on the Rasch Model. The Wright Map provides a picture by placing the difficulty of exam items on the same measurement scale as the ability of the candidates. Thus, one can evaluate how close the mean item measures is from the mean person measure, and how well distributed the range of items are in relation to the group of respondents, in order to suggest good or bad item-test targeting.

2.4. Summary of methods

Data collected from a previously existing database – the KPIC study (*described in Chapter 2.2*) – contributed to thesis studies on item generation (Chapter 3), item selection (Chapter 4) as well as construct- and predictive-validity (Chapters 4 and 5).

Chapter 6 utilizes a primary data source - the CAP-Knee study (*described in Chapter 6)* – designed primarily to achieve a key objective within this thesis: to explore the range of interpretations for items included within the developing CAP-Knee. By employing qualitative analytical approaches, Chapter *6* further details on item revision within the original version of the CAP-Knee, thus allowing creation of a final version of the questionnaire.

Finally, secondary analysis of data from the IMW&H study (*described in Chapter 7*), were employed for psychometric validation of the final version of the CAP-Knee (Chapter 7).

3. ITEM GENERATION: SELF-REPORT TRAITS ASSOCIATED WITH PERIPHERAL AND CENTRAL PAIN MECHANISMS.

3.1. Outline

This chapter outlines the evaluation of the KPIC baseline survey to identify items which measure traits that are associated with peripheral and/or central pain mechanisms on OA knee pain. This chapter discusses the statistical tests and expert assessment employed to select a shortlist of items from the original KPIC item pool (items = 104). The shortlist of items identified here will be considered for subsequent inclusion within the developing questionnaire.

3.2. Introduction

Pain in individuals with knee OA typically exists in a mixed state, in the presence of peripheral and other centrally acting mechanisms. Knee OA pain is perceived as originating from the joint (peripheral mechanisms), and are often associated with structural changes or inflammation, and exacerbated by joint loading and movement (Hunter, McDougall, & Keefe, 2008). Central mechanisms typically manifest at the spinal level and higher, and modulates the localized nociceptor input within the periphery, ultimately influencing the production or modulation of conscious pain response (Clauw & Hassett, 2017). In some cases however, these central mechanisms act disproportionately following persistent peripheral input and lead to a pathophysiological state of persistent pain (Graven-Nielsen & Arendt-Nielsen, 2002).

QST and imaging approaches (such as x-rays and fMRI) are typically employed as experimental markers to indicate changes in neural processing within the affected joint (*peripheral mechanisms*) and within the CNS (*central mechanisms*) (Cohen & Lee, 2015). Around 20% to 40% of individuals with knee OA pain show poor response to treatment targeted at the affected knee (e.g. total knee replacement surgery) (Kahlenberg et al., 2018), with poor outcomes linked to markers of central mechanisms (*as discussed in Chapter 1.5*) (Kahlenberg et al., 2018; Lewis, Rice, McNair, & Kluger, 2015; Petersen, Arendt-Nielsen, Simonsen, Wilder-Smith, & Laursen, 2015; Petersen, Graven-Nielsen, Simonsen, Laursen, & Arendt-Nielsen, 2016). This suggests that

underlying central mechanisms which might be augmenting the pain experience.

Optimal management of OA knee pain therefore requires that underlying pain mechanisms be identified in each individual (Allen et al., 2014). However, application of these approaches to clinical practice and population-based studies is limited, and traits linked to these QST and imaging measures are typically assessed on a case-by-case basis. Individual differences in self-report traits might also be associated with underlying mechanisms in individuals with knee pain (Brown et al., 2016; Campbell et al., 2015; Harden et al., 2003; Lluch et al., 2017; Lluch Girbes et al., 2016; Moreton et al., 2015; Moss et al., 2016; Riddle et al., 2010; Sullivan et al., 2009). Thus, a questionnaire-based approach to identifying these pain mechanisms might be beneficial in clinical and research-based settings, and may provide time and cost- efficiencies to the individuals with knee OA pain, as well as to the healthcare provider.

This study therefore hypothesizes that a shortlist of items which measure self-report traits that might reflect aspects of peripheral or central pain mechanisms can be identified in a sample of individuals aged 40 years and over, with knee pain, and with or without radiographic pathology within the affected knee.

3.3. Aims and Objectives

3.3.1. Aims

This study aims to generate a shortlist of self-report questions which reflect traits associated with underlying pain mechanisms.

3.3.2. Objectives

1. To identify items that most strongly represent traits suggested to reflect peripheral and/or central mechanisms of OA knee pain, by employing ESEM and assessment for item redundancy across item groups.
2. To assess content validity of questions based on expert consensus, in order to further shortlist items that represent traits suggested to reflect peripheral and/or central mechanisms of OA knee pain

3.4. Methods

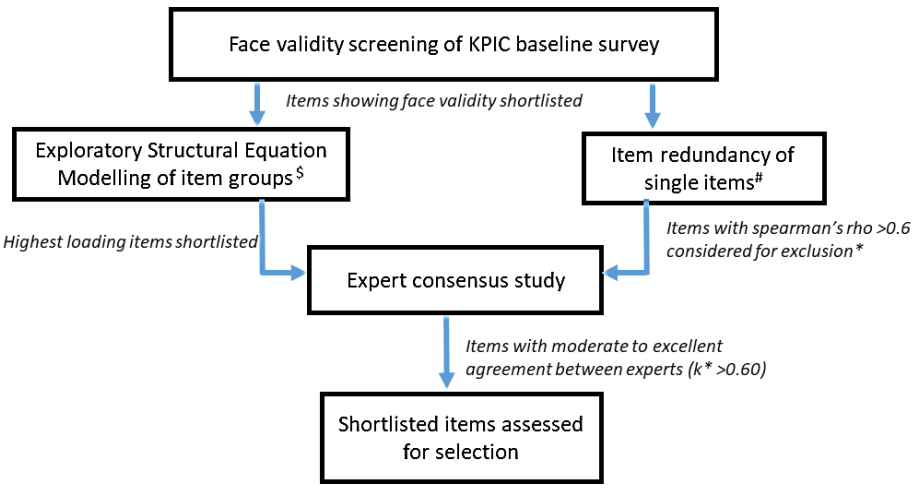
A series of methods illustrated in Figure 3-1 were applied in this chapter to allow generation of a shortlist of items from those originally included within the KPIC baseline survey. A key aim of the KPIC study is to define phenotypes that could assist clinicians and health care providers to select the most appropriate intervention for individual patients. The KPIC study therefore comprehensively assessed phenotypes shown in the literature to associate with knee pain. These included self-report and QST phenotypes linked to underlying pain mechanisms.

The self-report- and QST- traits assessed by the KPIC study were more comprehensive than those assessed in other large knee OA cohort studies, such as the Osteoarthritis Initiative (OAI) study, or the Cohort Hip and Cohort Knee (CHECK) study, which assess a less comprehensive set of traits. Thus, the comprehensive nature of the KPIC study, over and beyond other cohort studies, supports the use of the dataset in this thesis.

3.4.1. Participants

9506 individuals completed the Knee Pain and related health In the Community (KPIC) baseline survey, previously described in Chapter 2.2.4. 2152 participants reporting knee pain were included in this study.

Figure 3-1. Analytical methods employed for Item generation.



$Multiple items represented traits of (i) emotional wellbeing; (ii) catastrophic thinking; (iii) pain patterns; (iv) Neuropathic-like pain; (v) sleep/fatigue, traits previously linked to underlying knee OA pain mechanisms.
#Single items represented traits of (i) pain distribution and (ii) cognitive impact.
*Where redundancy was noted, one of the items was considered for exclusion following expert consensus study

In order to assess content validity of the shortlisted items, experienced clinical and research experts (n = 25) across various pain research disciplines (orthopaedics, rheumatology, sports and exercise medicine, psychology, neuroscience, physiotherapy, pharmacy, genetics and musculoskeletal epidemiology) within the Arthritis Research UK (ARUK) Pain Centre were invited by email to participate in the study.

3.4.2. KPIC baseline survey

Overall, the baseline KPIC baseline survey consisted of 115 items (Appendix 1, *p250*). Items included within the KPIC baseline survey existed either within established questionnaires, or existed as single items measuring specific traits. Questionnaire items were initially screened by the research team, and only those relevant to the project hypothesis were selected for inclusion. Items showing face validity for measures of broad traits which have previously been linked to clinical or experimental markers of central- or peripheral-mechanisms, including (i) emotional wellbeing; (ii) Catastrophic thinking; (iii) Pain pattern; (iv) Neuropathic-like pain; (v) Sleep/fatigue; (vi) Pain Distribution; and (vii) Cognitive impact, which were included within the KPIC baseline survey are described below:

3.4.2.1. Emotional wellbeing

Emotional wellbeing is an essential aspect of health as defined by the World Health Organization (Gureje, Von Korff, Simon, & Gater, 1998), and includes aspects relating to depression and anxiety amongst others.

Within the KPIC baseline survey, symptoms of anxiety and depression were measured using the HADS, and excludes items that may be related to other mood disorders like fatigue, headache or dizziness (Zigmond & Snaith, 1983). The HADS has been implemented to assess symptoms of depression or anxiety across knee OA pain populations, and has been linked to response to centrally acting treatment (Chappell et al., 2011; Chappell, Ossanna, & Liu-Seifert, 2009).

The HADS is comprised of a subscale for anxiety and for depression, with 7 items in each subscale. Each item is scored from 0 (no symptoms) to 3 (strong indication of symptoms) with each subscale scored 0-21. One group demonstrated the validity of the HADS by comparing the ability of subscales to

identify cases of anxiety or depression, in comparison to diagnoses made by interview (structured or semi structured) (Bjelland, Dahl, Haug, & Neckelmann, 2002). Both HADS subscales also correlate well with other scales designed to identify depression and anxiety, such as the Beck Depression Index, General Health Questionnaire, and the State Trait Anxiety Index, with correlation coefficients ranging from 0.34-0.83 for anxiety and 0.44-0.81 for depression demonstrating good concurrent validity (Bjelland et al., 2002).

3.4.2.2. Catastrophic thinking

Pain catastrophizing involves an exaggerated negative orientation toward noxious stimuli, and is typically measured using the 13- item PCS (Sullivan et al., 1995). The PCS is proposed to measure three subscales of rumination (4 items scored from 0-16), magnification (3 items scored from 0-12) and helplessness (6 items scored from 0-24) (Sullivan et al., 1995). Each item is scored on a 5-point Likert scale, from 0 (not at all) to 4 (all of the time; range 0-52. Individuals showing high catastrophic scores following completion of the PCS also discussed catastrophic thoughts and beliefs during participant interviews, while low scorers on the PCS discussed neutral thoughts (Sullivan et al., 1995). The PCS has been implemented to assess symptoms of catastrophic thinking in the knee pain population (Forsythe, Dunbar, Hennigar, Sullivan, & Gross, 2008).

3.4.2.3. Pain Patterns

The Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire is an 11-item tool designed to measure the two different patterns of knee pain, reported to be important by focus groups of people with constant and intermittent knee OA pain (Hawker et al., 2008). While there is no evidence to link any specific pain mechanisms to either constant or intermittent pain patterns, therapeutic studies in individuals with persistent moderate OA knee pain have demonstrated responsiveness of the total and subscale scores for the ICOAP following administration of duloxetine, a centrally acting treatment (Risser, Hochberg, Gaynor, D'Souza, & Frakes, 2013).

Eleven items on the ICOAP form two subscales considering both pain intensity and the effect of pain on quality of life (Hawker et al., 2008). Five items address constant pain and the remaining six items deal with intermittent pain. All items are measures on a five- point Likert scale. The response options for

the ICOAP items are 0 (Not at all), 1 (Mildly), 2 (Moderately), 3 (Severely) or 4 (Extremely).

3.4.2.4. Neuropathic-like pain

The modified PainDETECT questionnaire (mPDQ) was developed originally as a measure of symptoms linked to neuropathic-like pain reported by individuals with knee pain (Hochman et al., 2011).

The mPDQ comprises 12 items. The first three items assess current pain, strongest pain during the past 4 weeks, and average pain during the past 4 weeks. These items were measured on an 11-point numerical rating scale, scored from 0 (no pain) to 10 (pain as bad as it could be). These pain intensity ratings are not included within the total score. The fourth item includes a chart representation of four pain course patterns depicting persistence, fluctuation and attacks; the patients have to choose the one resembling their pain pattern the most. The selection of one of four pain course patterns has a value range of −1 to 1 and contributes to the total score. The fifth item asks patients about pain radiation with a yes/no response. Absence and presence of radiating pain has a value of 0 or 2, respectively. The remaining seven questions regarding the presence and severity of somatosensory signs and symptoms are rated on a six-category Likert scale (from never (0) to very strongly (5). One validation study within a knee OA pain population suggested that removal of the pain course item provided good evidence for questionnaire unidimensionality according to the Rasch model (Moreton et al., 2015).

3.4.2.5. Sleep/Fatigue

A four-item version of the MOS Sleep Scale was included within the KPIC study to assess theoretical dimensions of sleep: including sleep adequacy, sleep disturbance, sleep initiation, and somnolence (drowsy state) (Hay and Stewart, 1992). Participants were asked to respond on a six-point Likert scale score, ranging from 1 ‘none of the time’ to 6 ‘all of the time’. The 4 items included within the KPIC baseline survey included items from the original 12-item version (Hays et al., 2005), and the more recent 6- item version (Kim et al., 2013). Within the Observational Arthritis Study in Seniors (OASIS), sleep initiation problems measured within the Pittsburgh Sleep Quality Index (PSQI), were shown to occur at least weekly among 31% of individuals reporting knee pain or knee pain with radiographic evidence of OA (Wilcox et al., 2000).

Another group showed that the MOS sleep scale and PSQI are suitable for measuring the domains of sleep that are of particular importance in the study of pain (Cole, Dubois, & Kosinski, 2007). To assess fatigue in this study, the SF-12 items about having a lot of energy (Ware & Sherbourne, 1992), and another item about feeling tired, which were respectively measured on a 6- and 5- point Likert scale, were included in the ESEM analysis.

3.4.2.6. Pain Distribution

'Pain manikins', also referred to as 'pain drawings' or 'pain maps' have been used for the assessment for the location of painful bodily areas in patients since the 1940s (Ohnmeiss, 2000). Pain manikins are usually portrayed as an outline of the human figure on which patients shade the areas where they experience pain. Pain manikins allow documentation of pain location and pain distribution across chronic pain populations. Widespread pain distribution is typical of central sensitivity syndromes, such as fibromyalgia, and is therefore suggested to occur due to abnormal central sensitization to pain in individuals with localized musculoskeletal pain, such as knee pain (Croft, Jordan, & Jinks, 2005).

The 45- area grid methodology (Appendix 2.1., *p273*) described by Croft et al (2005) was employed to identify painful areas within the KPIC baseline survey.

3.4.2.7. Cognitive impact

One item ("Does your pain or other bodily symptoms stop you from concentrating on what you are doing") assessing the cognitive impact item of bodily symptoms, or pain, originated from the illness behaviour subscale of the IAS (Ferguson & Daniel, 1995). Scores from this subscale have been demonstrated to predict the onset of new chronic widespread pain in community dwelling individuals (Gupta et al., 2007).

Cognitive impairments have been demonstrated in central sensitization syndromes, such as fibromyalgia (Rodriguez-Andreu et al., 2009). In addition, cognitive behavioural therapy (CBT) aimed towards addressing cognitive factors including maladaptive behaviour patterns such as avoidance behaviours has been shown to reduce pain severity (O'Moore et al., 2018). In individuals with fibromyalgia, CBT is also linked to increased activity in brain regions associated with executive cognitive control, or regions associated with

psychological traits linked to central mechanisms of pain (Jensen et al., 2012). Together, these findings suggest a relationship between measures linked to cognitive symptoms and other traits linked centrally mediated pain.

This item was included in the current study and like other items originating from the illness behaviour subscale, was measured on a 5- point Likert scale (0= 'No'; 1= 'Rarely'; 2= 'Sometimes', 3 = 'Often', 4 = 'Most of the time').

3.4.3. Expert Survey

Based on academic and/or clinical expertise in knee OA pain, experts conducting research within the Versus Arthritis Pain Centre in July 2016 were asked to rate each of the items shortlisted following initial item generation analysis. Of the 25 experts invited via email to complete the expert survey study, 17 experts responded, including Epidemiologists (n=2), Consultant orthopaedic surgeon (n=1), Consultant rheumatologists (n=3), Arthritis pain researchers (n=3), Psychologists (n=3), Neuroscientists (n=2), Pharmacist (n=1), and Physiotherapists (n=2). Average response time was 8 days.

For each item included within the survey sent to experts, the degree of relevance to which each item reflected predominantly central and peripheral mechanisms of knee pain were rated by experts, using a four-point Likert scale (0= not at all relevant; 1=slightly relevant; 2=moderately relevant; 3=highly relevant). Subscales were provided for peripheral and central mechanisms of knee pain. Questionnaires and relevant study documents are included within Appendix 8 *(p337* to *p339*).

3.5. Statistical Analysis

The statistical approaches applied in this study are detailed below. Firstly, ESEM was employed to refine the large KPIC item pool by identifying the traits measured by included questionnaires. ESEM analysis allowed identification of the most representative items for each of the identified traits. Next, traits measured by single items, were assessed using correlation analysis to identify whether any redundancy existed across these items. Where redundancy was found, these items were considered for exclusion from the item pool. Finally, shortlisted items were assessed for content validity by assessing expert ratings on the relevance of each item to peripheral- and central- mechanisms.

Items deemed to show content validity were considered for further testing, and thus, for inclusion within the final tool developed within this thesis.

3.5.1. Exploratory Structural Equation Modelling (ESEM)

Analysis described in this chapter was conducted within the KPIC knee pain population (n=2152). ESEM was employed to reduce the item pool by identifying the most representative items for each of the relevant traits measured within the KPIC baseline survey. The KPIC survey contained questionnaires containing a large set of diverse items, ESEM was used to look for sets of items which could be representative of different traits linked to central knee OA pain mechanisms. ESEM was conducted within each of the item group measured by multiple items or established questionnaires included within the KPIC baseline survey, including emotional wellbeing, catastrophic thinking, pain patterns, neuropathic-like pain, and sleep/fatigue. To identify items for further shortlisting, item-loading scores for each identified latent trait were examined during the analysis. The two items with the highest loading to the identified latent trait were shortlisted for further analyses.

As described within Chapter 2.3.2.1, ESEM model fit was determined by the Comparative fit index (CFI), Tucker Lewis Index (TLI), the root mean square error of approximation (RMSEA) and the weighted root mean residual (WRMR). Acceptable model fit was determined by a CFI and TLI >0.96, and RMSEA < 0.08 (Hooper et al., 2008).

ESEM was conducted using M*Plus* 7 (Muthén, 2012), with a complex survey design routine used to account for clustering amongst GPs. The model with the cleanest factor structure with item loadings above 0.30, no or few item cross loadings (*item loading >0.3 to another identified trait*), no factors with fewer than three items- were deemed to have best fit to the data (Jason W. Osborne, Anna B. Costello, & Kellow, 2008).

. Standardized factor loadings are presented in this study. Polyserial factor correlation between the identified latent factors in each item group are also reported.

3.5.2. Item Redundancy

Traits of cognitive impact and pain distribution and were only measured by an individual item and could not be entered into ESEM analysis. In order to establish that both of these items measured separate traits, a test for redundancy was conducted by employing spearmans correlation. Where greater than moderate correlation was identified (spearman's rho >0.6), one of the items was considered for exclusion following expert consensus.(Taber, 2018).

3.5.3. Inter-rater agreement

In order to establish content validity of the items shortlisted following ESEM and item redundancy analysis, items were rated on a 4-point Likert scale (0= not at all relevant; 1=slightly relevant; 2=moderately relevant; 3=highly relevant) by experts within the ARUK pain centre. Content validity pertains to the degree to which the instrument fully assesses or measures the construct of interest.(DeVon et al., 2007; Polit & Beck, 2006; Sangoseni, Hellman, & Hill, 2013). The development of a content valid instrument is typically achieved by a rational analysis of the instrument by raters (experts) familiar with the construct of interest or experts on the research subject (DeVon et al., 2007; Polit & Beck, 2006; Sangoseni et al., 2013).

One proportion agreement method to assess ratings provided by experts, the item Content Validity Index (-ICVI) – Equation 1, quantitatively estimates the content validity of the items (Lynn, 1986; Polit, Beck, & Owen, 2007). To control for high proportion of agreement due to random chance, calculation of the probability of chance (Equation 2) and modified Kappa statistics (Equation 3) and are recommended.

Chance agreement is an issue of concern in evaluating indexes of inter-rater agreement, especially when the choices are dichotomous, as is the case when 4-point ratings are collapsed into the two categories of relevant and not relevant. The modified kappa statistic (k^*) was computed to evaluate whether expert consensus for each item was poor (*below 0.40*), fair (*0.41 to 0.60*), moderate (*0.61 to 0.80)* or excellent (*0.90 and above*) (Cicchetti & Sparrow, 1981; Fleiss, 1981).

Equation 1 Item Content Validity Index.

$$I - CVI\ (peripheral) = \frac{Number\ of\ experts\ rating\ item > 2}{total\ number\ of\ experts}$$

Equation 2 Probability of Chance.

$$^{N}pc = \left[\frac{N!}{A!(N-A)!}\right].5$$

Where N= number of experts, and A= Number agreeing on relevance. *k** was then analysed using the Equation 3:

Equation 3 Modified Kappa.

$$modified\ kappa\ (k^*) = \frac{ICVI - Pc}{1 - Pc}$$

For both central and peripheral subscales, (I-CVI and k* are presented for each item. In this study, items which demonstrate moderate to excellent agreement between experts (k* >0.60) were shortlisted for further investigation.

3.6. Results

3.6.1. Participants Characteristics

Means and standard deviations (SDs) for participant demographics are shown below in Table 3-1.

3.6.2. ESEM

Fit statistics for the competing factor models within each multiple item group are described below:

3.6.2.1. Emotional wellbeing items

The two- and three-factor model showed good fit to the data, with the one-factor models showing significantly poorer model fit within the exploratory data (Table 3-2). Models with more latent traits specified performed significantly better ($p<0.01$) than competing models with a lower number of traits specified.

Table 3-1. Demographics, questionnaire and item scores for participants reporting knee pain in the KPIC baseline population.

	Knee Pain (n=2152)
Women (%)	1226 (57%)
Age (years ± SD)	61.90 ±10.44
BMI (kg/m^2 ± SD)	28.55 ±5.77
Questionnaire Scores	
HADS – Anxiety (Out of 21)	9 (8 to 11)
HADS – Depression (Out of 21)	9 (8 to 10)
Pain Catastrophizing Scale (Out of 52)	7 (2 to 17)
Intermittent ICOAP (Out of 100)	14 (7 to 25)
Constant ICOAP (Out of 100)	21 (4 to 42)
Modified PainDETECT Questionnaire (Out of 38)	7 (3 to 12)
Item Scores	
Cognitive Impact (Out of 4)	2 (1 to 3)
Fatigue item 1 (Out of 5)	3 (2 to 4)
Fatigue item 2 (Out of 6)	3 (2 to 5)
Sleep Adequacy item (Out of 6)	4 (2 to 5)
Sleep Disturbance item (Out of 6)	6 (5 to 6)
Sleep Initiation item (Out of 6)	5 (3 to 6)
Somnolence Item (Out of 6)	5 (4 to 6)
Pain Distribution (Out of 45 sites)	4 (2 to 9)

Medians and Inter-Quartile Range (IQR) reported for questionnaire and item scores. BMI (Body Mass Index); HADS-Anxiety (Hospital Anxiety and Depression Scale, Anxiety subscale); HADS-Depression (Hospital Anxiety and Depression Scale, Depression subscale); Intermittent ICOAP (Intermittent and Constant Osteoarthritis Pain – Intermittent subscale); Constant ICOAP ((Intermittent and Constant Osteoarthritis Pain – Constant subscale).

Table 3-2. Goodness-of-fit statistics for the competing factor models in the 14-item emotional wellbeing item group

Fit Indices	Competing Factor Models			
	I factor	2 factor	**3 factor**	4 factor
CFI	0.919	0.985	**0.994**	0.998
TLI	0.904	0.979	**0.989**	0.995
RMSEA	0.073	0.035	**0.025**	0.018
X^2 (df)	972 (77)	220 (64)	**119 (52)**	104.229 (62)

CFI=Comparative Fit Index; TLI – Tucker Lewis Index; RMSEA = Root Mean Square Error of Approximation; X^2(df)= Chi Square(degree of freedom).
Column in bold represents the accepted model for the item group.

The four-factor model explained the data significantly better than the competing one-, two-, and three- factor models (*p<0.0005*). However, there was a much clearer distinction between factors in the three- factor model, compared to the four-factor model, which only had two items with loadings greater that 0.3 on the fourth factor (Appendix 9.1, *p347*).

Positive polyserial factor correlation (rho range: 0.541 to 0.604, p<0.001) was identified across all identified factors. Thus the three factor model was retained.

The two highest loading items for each of the three identified latent traits of depression (“I still enjoy the things I used to enjoy” and “I look forward with enjoyments to things”), anxiety (“I get a sort of frightened feeling as if something awful is about to happen” and “I get sudden feelings of panic”) and psychomotor agitation (“I can sit at ease and feel relaxed” and “During the past month, have you felt calm or peaceful?”) were shortlisted for further assessment – Table 3-3. These items loaded distinctly on to their respective factors.

3.6.2.2. Catastrophic thinking items

The two- and three- factor model showed good fit to the data, with the one-factor model showing the poorest model fit (Table 3-4).

Table 3-3. Standardized item loadings for the three-factor model in emotional wellbeing item group.

Items	Factor 1 (Depression)	Factor 2 (Anxiety)	Factor 3 (Psychomotor Agitation)
I feel tense or wound up	0.139*	0.475***	0.323***
I still enjoy the things I used to enjoy	**0.828*** **	-0.142**	-0.012
I get a sort of frightened feeling as if something awful is about to happen	0.057	**0.828*** **	-0.009
I can laugh and see the funny side of things	0.696***	0.017*	0.163***
Worrying thoughts go through my mind	0.035	0.746***	0.152*
I feel cheerful	0.686***	0.039	0.151***
I can sit at ease and feel relaxed	0.414***	0.010	**0.549*** **
I feel as if I am slowed down	0.235*	0.255***	-0.135
I get a sort of frightened feeling like ‘butterflies’ in the stomach	-0.018	0.607***	-0.205**
I have lost interest in my appearance	0.600***	0.024	-0.003

Table continued on next page
p<0.05 **p<0.01 *** p<0.001
Items in bold shortlisted for further assessment

Table 3-3(Cont.). Standardized item loadings for the three-factor model in emotional wellbeing item group.

Items	Factor 1 (Depression)	Factor 2 (Anxiety)	Factor 3 (Psychomotor Agitation)
I feel restless as if I have to be on the move	-0.044	0.196***	**0.477*** **
I look forward with enjoyments to things	**0.942*** **	-0.083	0.006
I get sudden feelings of panic	-0.018	**0.799*** **	0.113
I can enjoy a good book or radio or television programme	0.435***	-0.123**	0.396***

p<0.05 **p<0.01 *** p<0.001
Items in bold shortlisted for further assessment

The three-factor model significantly fit the data better than the one- and two-factor models (p<0.0005), however, the three- factor model was rejected as a result of only two items showing loadings greater that 0.3 on the third identified factor. A strong positive polyserial factor correlation (rho = 0.862, p<0.001) was identified between both identified factors. A distinct loading pattern was observed for the best fitting two-factor model (Table 3-5). Factors of "helplessness", and "rumination" showed distinct factors loadings (loading >0.3). The two highest loading items for each of the identified latent factors of Helplessness ("I feel I can't go on" and "I feel I can't stand it anymore"), and rumination ("I keep thinking about how much it hurts" and "I can't seem it keep it out of my mind") were shortlisted for further assessment. These items loaded distinctly on to their respective factors, unlike the three-factor model (Appendix 9.2, *p347*).

3.6.2.3. Pain Pattern

Poor fit was identified for models that included all the ICOAP items together, hence items measuring constant- and intermittent- pain were entered into separate models. For both subscales, the two-factor models showed excellent fit for the data and significantly altered the one-factor model fit (p<0.0001)- Table 3-6. However, there was significant cross-loading between factors in the two- factor models for both subscales (Appendix 9.3, *p349* and Appendix 9.4, *p350*), thus the two factor models were rejected.

Table 3-4. Goodness-of-fit statistics for the competing factor models in the 13-item catastrophic thinking item group.

Fit Indices	**Competing Factor Models**		
	I factor	**2 factor**	3 factor
CFI	0.99	**0.99**	0.99
TLI	0.99	**0.99**	0.99
RMSEA	0.06	**0.04**	0.04
X2 (df)	592 (65)	**254 (53)**	182 (42)

CFI=Comparative Fit Index; TLI – Tucker Lewis Index; RMSEA = Root Mean Square Error of Approximation; X2(df)= Chi Square(degree of freedom).
Column in bold represents the accepted model for the item group.

Table 3-5. Standardized item loadings for the two-factor model in catastrophic thinking item group.

Items	Factor 1 (Helplessness)	Factor 2 (Rumination)
I worry all the time about whether the pain will end	0.470*	0.395*
I feel I can‘t go on	**1.000***	-0.131***
It’s terrible and I think it’s never going to get any better	0.858*	0.074
It’s awful and I feel that it overwhelms me	0.871*	0.101**
I feel I can’t stand it anymore	**0.932***	-0.001
I become afraid that the pain will get worse	0.495*	0.384*
I keep thinking of other painful events	0.460*	0.361*
I anxiously want the pain to go away	0.069	0.814*
I can’t seem it keep it out of my mind	0.000	**0.921***
I keep thinking about how much it hurts	-0.169*	**1.000***
I keep thinking about how badly I want the pain to stop	0.041	0.901*
There’s nothing I can do to reduce the intensity of the pain	0.310*	0.542*
I wonder whether something serious may happen	0.240**	0.519*

Table continued on next page
*p<0.001 **p<0.01 ***p<0.05
Items in bold shortlisted for further assessment.

Table 3-6. Goodness-of-fit statistics for the competing factor models in the pain pattern item group.

	Competing Factor Models					
Fit Indices	Total ICOAP – 1 factor	Total ICOAP – 2 factor	**Constant ICOAP – 1 factor**	Constant ICOAP – 2 factor0	**Intermittent ICOAP – 1 factor**	Intermittent ICOAP – 2 factor
CFI	0.99	0.99	**0.998**	1.00	**0.996**	1.00
TLI	0.99	0.99	**0.997**	1.00	**0.994**	0.99
RMSEA	0.16	0.133	**0.094**	0.014	**0.17**	0.06
X2 (df)	843 (44)	449 (34)	**38.9 (5)**	1.151 (1)	**22.2 (9)**	15.8 (4)

CFI=Comparative Fit Index; TLI – Tucker Lewis Index; RMSEA = Root Mean Square Error of Approximation; X2(df)= Chi Square(degree of freedom).
Column in bold represents the accepted model for the item group.

As shown in Table 3-7 and Table 3-8, the two highest loading items for each of the identified latent traits of constant pain ('In the past week, how much has your constant knee pain affected your sleep?' and 'In the past week, how frustrated or annoyed have you been by your constant knee pain?') and intermittent pain ('In the past week, how much has your knee pain that comes and goes affected your sleep?' and 'In the past week, how upset or worried have you been by your knee pain that comes and goes?') were shortlisted for further analysis.

3.6.2.4. Neuropathic-like pain

The three-factor model significantly fit the data better than the one- and two-factor models ($p<0.0001$) – Table 3-9

Positive polyserial factor correlation (rho range: 0.461 to 0.748, $p<0.001$) was identified across all three identified factors.

As shown in Table 3-10, the two highest loading items for each of the identified latent factors of pain intensity ("In the past month. How intense was your worst knee pain rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'?" and "In the past month, on average, how intense was the pain in your most painful knee rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'?"), spontaneous- ("Do you have a tingling or prickling sensation in the area of your most painful knee 'pain' (like crawling ants or electrical tingling)?" and "Do you suffer from a burning sensation (e.g., stinging nettles) in or around your most painful knee?") and evoked-neuropathic pain symptoms ("Is cold or heat (bath water) in this area occasionally painful?" and "Is light touching (clothing, a blanket) in this area painful?") were shortlisted for further assessment.

These items loaded distinctly on to their respective factors and did not show any cross loading across the other identified latent factors. No item showed significant loading on the fourth factor in the four-factor model (Appendix 9.5, *p351*).

Table 3-7. Standardized item loadings for the one-factor model in constant pain item group.

Items	Factor 1 (Constant pain)
In the past week, how intense has your constant knee pain been?	0.933*
In the past week, how much has your constant knee pain affected your sleep?	**0.953***
In the past week, how much has your constant knee pain affected your overall quality of life?	0.862*
In the past week, how frustrated or annoyed have you been by your constant knee pain?	**0.948***
In the past week, how upset or worried have you been by your constant knee pain?	0.918*

*p<0.001 **p<0.01 ***p<0.05
Items in bold shortlisted for further assessment.

Table 3-8. Standardized item loadings for the one-factor model in intermittent pain item group.

Items	Factor 1 (Intermittent pain)
In the past week, how intense has your most severe knee pain that comes and goes been?	0.901*
In the past week, how much has your knee pain that comes and goes affected your sleep?	**0.941***
In the past week, how much has your knee pain that comes and goes affected your overall quality of life?	0.825*
In the past week, how frustrated or annoyed have you been by your knee pain that comes and goes?	0.936*
In the past week, how upset or worried have you been by your knee pain that comes and goes?	**0.948***
In the past week, how frequently has this knee pain that comes and goes occurred?	0.925*

*p<0.001 **p<0.01 ***p<0.05

Items in bold shortlisted for further assessment.

Table 3-9. Goodness-of-fit statistics for the competing factor models in the 12-item neuropathic-like pain item group.

	Competing Factor Models			
Fit Indices	I factor	2 factor	**3 factor**	4 factor
CFI	0.858	0.960	**0.988**	0.992
TLI	0.823	0.935	**0.973**	0.973
RMSEA	0.105	0.065	**0.042**	0.041
X2 (df)	368 (44)	130 (34)	**54 (25)**	36 (17)

CFI=Comparative Fit Index; TLI – Tucker Lewis Index; RMSEA = Root Mean Square Error of Approximation; X2(df)= Chi Square(degree of freedom).
Column in bold represents the accepted model for the item group.

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Table 3-10. Standardized item loadings for the three-factor model in neuropathic-like pain item group.

Items	Factor 1 (Pain Intensity)	Factor 1 (Spontaneous symptoms)	Factor 1 (Evoked symptoms)
Over the past month, does your pain run up and down your leg?	0.218*	0.424*	0.033
How would you rate your most painful knee pain on a 0-10 scale at the present time, that is right now, where 0 is 'no pain' and 10 is 'pain as bad as could be'?	0.664*	0.063	0.109***
In the past month. How intense was your worst knee pain rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'?	**0.926***	-0.006	-0.005
In the past month, on average, how intense was the pain in your most painful knee rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'?	**0.959***	-0.005	-0.023
The next question is on the pattern of your pain in your most painful knee. Which if the 4 different options below is the one that best describes the pattern of your worst knee pain over the past month?	-0.283*	0.043	-0.273
Do you suffer from a burning sensation (e.g., stinging nettles) in or around your most painful knee?	0.100***	**0.710***	0.007*

Table continued on next page
*p < 0.001 **p<0.05
Items in bold shortlisted for further assessment.

Table 3-10(Cont.). Standardized item loadings for the three-factor model in neuropathic-like pain item group.

Items	Factor 1 (Pain Intensity)	Factor 1 (Spontaneous symptoms)	Factor 1 (Evoked symptoms)
Do you have a tingling or prickling sensation in the area of your most painful knee 'pain' (like crawling ants or electrical tingling)?	0.001	**1.000***	-0.226***
Is light touching (clothing, a blanket) in this area painful?	0.149**	0.191*	**0.559***
Do you have sudden pain attacks in the area of your pain, like electric shocks?	0.237*	0.240*	0.177**
Is cold or heat (bath water) in this area occasionally painful?	0.001	0.002	**0.861***
Do you suffer from a sensation of numbness in the areas that you marked?	-0.102***	0.400*	0.361*
Does slight pressure in this area, e.g., with a finger, trigger pain?	0.152	0.001	0.520*

*p < 0.001 **p<0.05
Items in bold shortlisted for further assessment.

3.6.2.5. Sleep/Fatigue

The two-factor model significantly fit the data better than the one- and two-factor models (p<0.0001) – Table 3-11. However, only one item loaded onto the second factor (Appendix 9.6, *p353*). Thus the 2 item-model was rejected. Items representing fatigue showed the highest loading scores to the identified latent and were therefore selected for further assessment - Table 3-12.

Table 3-11. Goodness-of-fit statistics for the competing factor models in the 6-item sleep/fatigue item group..

	Competing Factor Models	
Fit Indices	**I factor**	2 factor
CFI	**0.979**	0.988
TLI	**0.966**	0.954
RMSEA	**0.096**	0.112
X2 (df)	**179(9)**	106.8(4)

CFI=Comparative Fit Index; TLI – Tucker Lewis Index; RMSEA = Root Mean Square Error of Approximation; X2(df)= Chi Square(degree of freedom).
Column in bold represents the accepted model for the item group

3.6.3. Item redundancy

No item redundancy (rho<0.6) was identified in the spearman's correlation analysis between the cognitive impact and pain distribution item. These items showed moderate strengths of correlation (spearman's rho = 0.536; p = 0.032).

3.6.4. Inter-rater agreement

Experts within the ARUK pain centre were recruited to rate the relevance of the 24 shortlisted items in measuring self-report traits relevant to peripheral and central mechanisms of knee OA pain.

3.6.4.1. Items measuring peripheral pain mechanisms

2 items measuring latent traits of pain intensity originating from the neuropathic pain symptoms item group showed moderate to excellent

agreement (k* range > .60) in measuring self-report traits relevant to peripheral mechanisms of knee OA pain (Table 3-13).

Table 3-12. Standardized item loadings for the one-factor model in fatigue/sleep item group.

Items	Factor 1 (Fatigue)
How often during the past 4 weeks did you get enough sleep to feel rested in the morning?	0.675*
How often during the past 4 weeks did you awaken short of breathe or with a headache?	0.517*
How often during the past 4 weeks did you have trouble falling asleep?	0.536*
How often during the past 4 weeks did you have trouble staying awake during the day?	0.642*
In the past month, did you feel tired on most days?	**0.873***
During the past month, Did you have a lot of energy?	**0.707***

* p<0.001
Items in bold shortlisted for further assessment.

3.6.4.2. Items measuring central pain mechanisms

17 items showed moderate to excellent agreement (k* > .60) in measuring latent traits relevant to central mechanisms of knee OA pain. 17 of the 19 items originated from established questionnaires previously shown to measure latent traits of anxiety, depression, helplessness, rumination, fatigue, spontaneous and evoked neuropathic pain symptoms, and constant and intermittent pain patterns (identified in Chapter 3.6.2). Self-report items representing pain distribution and cognitive impact, also showed moderate to excellent agreement (k* > .60) in measuring traits relevant to central mechanisms of knee OA pain (Table 3-13).

Table 3-13. Expert ratings for each item as a measure of underlying pain mechanisms.

Item description	Peripheral subscale			Central Subscale		
	Sum of raters	I-CVI	k*	Sum of raters	I-CVI	k*
Over the past month, do you have a tingling or prickling sensation in the area of your most painful knee 'pain' (like crawling ants or electrical tingling)?	15	0.4	0.39	**15**	**0.67**	**0.66**
Number of painful body regions (shaded on body pain manikin)	14	0.28	0.28	**16**	**0.81**	**0.81**
In the past month. How intense was your worst knee pain rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'?	14	0.71	0.71	14	0.42	0.42
In the past week, how much has your constant knee pain affected your sleep?	12	0	-	**14**	**0.64**	**0.64**
In the past month, did you feel tired on most days?	12	0	-	**13**	**0.61**	**0.61**
Over the past month in your most painful knee, is light touching (clothing, a blanket) in this area painful?	15	0.46	0.46	**15**	**0.80**	**0.79**

Table continued on next page

I-CVI = Item Content Validity Index; k*= modified kappa ('-' = Values cannot be derived when I-CVI = 0)

Rows in bold represent items showing moderate to excellent agreement for peripheral or central mechanisms.

Table 3-13(Cont.). Expert ratings for each item as a measure of underlying pain mechanisms.

Item description	Peripheral subscale			Central subscale		
	Sum of raters	I-CVI		Sum of raters	I-CVI	
Please indicate how often the statement below applies to you: "I look forward with enjoyment to things"	14	0.07	0.07	14	**0.64**	**0.64**
In your most painful knee, over the past month, is cold or heat (bath water) in this area occasionally painful?	15	0.26	0.26	15	**0.73**	**0.73**
How much time during the past month did you have a lot of energy?	15	0.13	0.13	14	0.57	0.57
In the past week, how upset or worried have you been by your knee pain that comes and goes?	13	0	-	13	**0.69**	**0.69**
Please indicate what degree the statement below applies to your painful experience: "I can't seem it keep it out of my mind"	13	0	-	14	**0.71**	**0.71**
In the past month, on average, how intense was the pain in your most painful knee rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'?	**14**	**0.78**	**0.78**	14	0.42	0.42

Table continued on next page
I-CVI = Item Content Validity Index; k*= modified kappa ('-' = Values cannot be derived when I-CVI = 0)
Rows in bold represent items showing moderate to excellent agreement for peripheral or central mechanisms.

Table 3-13(Cont.). Expert ratings for each item as a measure of underlying pain mechanisms.

Item description	Peripheral subscale			Central Subscale		
	Sum of raters	I-CVI	k*	Sum of raters	I-CVI	k*
Please indicate how often the statement below applies to you: "I get a sort of frightened feeling as if something awful is about to happen"	12	0	-	**13**	**0.69**	**0.69**
Does your pain or other bodily symptoms stop you from concentrating on what you are doing?	13	0.07	0.07	**14**	**0.71**	**0.71**
Please indicate how often the statement below applies to you: "I still enjoy the things I used to enjoy"	13	0	-	**14**	**0.71**	**0.71**
Please indicate what degree the statement below applies to your painful experience: "I keep thinking about how much it hurts"	11	0.18	0.18	**12**	**0.83**	**0.83**
In the past week, how frustrated or annoyed have you been by your constant knee pain?	14	0.42	0.42	15	0.6	0.59
Please indicate what degree the statement below applies to your painful experience: "I feel I can't stand it anymore"	13	0.07	0.07	**14**	**0.78**	**0.78**

Table continued on next page

I-CVI = Item Content Validity Index; k*= modified kappa ('-' = Values cannot be derived when I-CVI = 0)

Rows in bold represent items showing moderate to excellent agreement for peripheral or central mechanisms.

Table 3-13(Cont.). Expert ratings for each item as a measure of underlying pain mechanisms.

Item description	Peripheral subscale			Central Subscale		
	Sum of raters	I-CVI	k*	Sum of raters	I-CVI	k*
In the past week, how much has your knee pain that comes and goes affected your sleep?	13	0.07	0.07	**14**	**0.64**	**0.64**
Over the past month, do you suffer from a burning sensation (e.g., stinging nettles) in or around your most painful knee?	14	0.35	0.35	15	0.6	0.59
Please indicate how often the statement below applies to you: "I can sit at ease and feel relaxed"	13	0.07	0.07	14	0.57	0.57
Please indicate how often the statement below applies to you: "I get sudden feelings of panic"	12	0	-	13	**0.61**	**0.61**
Please indicate what degree the statement below applies to your painful experience: "I feel I can‘t go on"	13	0.07	0.07	14	**0.78**	**0.78**
Please indicate how often the statement below applies to you:“I feel restless as if I have to be on the move.”	13	0	-	13	0.46	0.46

Table continued on next page

I-CVI = Item Content Validity Index; k*= modified kappa (‘-‘ = Values cannot be derived when I-CVI = 0)

Rows in bold represent items showing moderate to excellent agreement for peripheral or central mechanisms.

3.7. Results Summary

Based on ESEM and expert consensus, 17 items measuring broad traits of catastrophizing, psychological well-being, constant pain, intermittent pain, fatigue, neuropathic symptoms, pain distribution, and cognitive impact have been shown to have content validity in reflecting central pain mechanisms associated within knee OA pain. These 17 items were more strongly associated with their respective latent traits, compared to other items identified after initial screening of the KPIC survey. Thus, these items were shortlisted for further analysis aimed at developing a self-report measure of central mechanisms in individuals with knee OA pain.

The 2 items suggested to measure traits linked to peripheral mechanisms (pain intensity) are yet to be linked to any relevant markers such as presence of osteophytes. These items were thereby excluded from further analyses.

4. ITEM SELECTION: SELF-REPORT TRAITS ASSOCIATED WITH A QST MEASURE OF CENTRAL PAIN MECHANISMS.

4.1. Outline

This chapter reports the selection of items most representative of traits associated with central mechanisms of knee OA pain for inclusion within the developing questionnaire. The use of PPTs at a distal site –- a QST index for central pain mechanisms –- are also discussed here. PPTs were analysed against reports of pain distribution, as indicated by participants on the body pain manikin, in order to quantify pain distribution within the developing questionnaire. The strength of association between self-report traits measured by shortlisted items and host questionnaires, with PPTs, were sought.

A priori developed criteria, such as a lack of association ($p<0.05$) between PPTs and traits measured by shortlisted items and host questionnaires, were applied across the item pool to select the most representative item for each self-report trait.

4.2. Introduction

QST can indicate changes in pain sensitivity, with PPTs being the most commonly used method for assessing sensitization. PPT might be reduced at a site of clinical pain, suggesting neuronal sensitization of the affected area. More widespread increased sensitivity at pain-free control sites is suggestive of altered pain processing in the CNS (Croft et al., 2005; Graven-Nielsen & Arendt-Nielsen, 2002). In animal models of OA, pain sensitivity (*reduced withdrawal thresholds to punctate stimulation*) at a site distal to the affected knee (*hindpaw*) is characterized by spinal hyperexcitability of neurons innervating sites distal to the affected joint (Fernihough et al., 2004; Neugebauer, Lucke, & Schaible, 1993; Sagar et al., 2010; Schaible, Ebersberger, & Von Banchet, 2002). Descending pain control mechanisms (as discussed in Chapter 1.4.3.2) have been implicated as a central mechanism for widespread pain in individuals with fibromyalgia (Bosma et al., 2016), and has further been associated with pain sensitivity distal to the affected joint in people with OA (Gwilym et al., 2009).

Individual differences in self-report traits identified in the previous chapter (Chapter 3.6) have also been associated with knee pain severity (Carlesso et al., 2016; Croft et al., 2005; Hadlandsmyth et al., 2017; Hochman et al., 2011; Riddle et al., 2010; Snijders et al., 2011; Somers et al., 2009). High scores on questionnaires which measure these traits, and low PPTs, have been shown to predict poor outcome following treatment directed to the painful knee (Ali, Lindstrand, Sundberg, & Flivik, 2017; Petersen et al., 2015; Petersen et al., 2016; Wylde et al., 2017; Wylde et al., 2011). These might indicate associations between self-report traits, PPTs and underlying central mechanisms in individuals with knee pain. However, using a full battery of existing questionnaires, plus PPT measurement would be resource intensive during normal clinical encounters.

While a variety of individual questionnaires exist which measure many of these self-report traits that have previously been linked to central mechanisms of pain, no clinically useful method exists for quantifying pain distribution. One group found that knee pain plus 'pain in ≥ 2 areas other than the knee' had 4 times the odds of being depressed than those reporting no pain at all (Croft et al., 2005). Number of painful sites shaded on the pain manikin has also been reported to be independently associated with poorer mental and physical health-related quality of life (Dave et al., 2015). Widespread pain distribution is a key symptom observed in a fibromyalgia, a disease characterized by the presence of CS. While expanded pain distribution is considered a sign of CS, there are no studies to support associations between CS measures and expanded pain distribution in individuals with knee OA pain.

Thus, this study hypothesizes that it is possible to select a concise set of self-report questions which measure traits that are associated with central pain mechanisms. This study further hypothesizes that pain distribution is a potentially useful clinical trait for classifying underlying central pain mechanisms, and that an optimum classification criterion for pain distribution can be identified in individuals reporting knee pain.

4.3. Aims and Objectives

4.3.1. Aims

Overall, this study aimed to select a valid set of self-report questions that measure a singular trait associated with central pain augmentation, as indicated by reduced PPT at the proximal tibia, a site distal to the painful knee.

This study secondarily aimed to determine whether self-reported pain distribution, using a pain manikin, is associated with PPTs in people with knee pain. Further, this study sought to define the optimal manikin-derived measure as an index of augmented central pain processing.

4.3.2. Objectives

1. In order to effectively quantify pain distribution in identify central knee OA pain mechanisms, associations between PPTs and pain distribution will be assessed, and an optimal cut off for central pain mechanisms using the body pain manikin will be determined..
2. In order to select traits for inclusion within the developing tool, associations between PPTs and self-report measures will be assessed. A priori criteria (Figure 4-1) will be assessed across items to select best performing items representing traits which are significantly linked to PPTs.
3. In order to determine construct validity of the selected items, each item representing a respective trait significantly linked to PPTs, will undergo factor analysis.

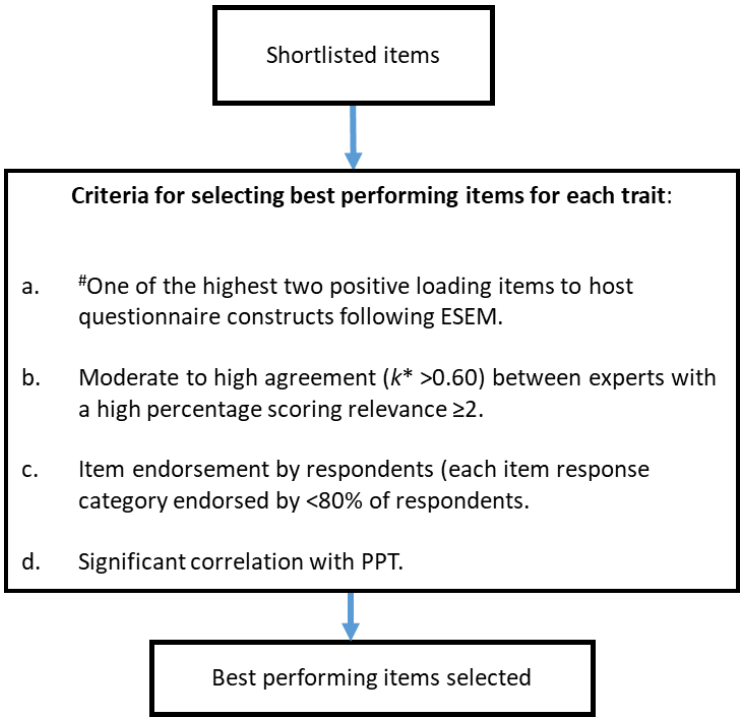
4.4. Methods

4.4.1. Participants

The KPIC survey at baseline assessed various pain related traits in individuals aged 40 years and over – see Chapter 2.2.5. Of the initial 9506 baseline respondents, 420 participants were invited for further radiographic and psychophysical assessment. Three distinct groups comprising of individuals with no knee pain (n=98), early knee pain (n=219) or established knee pain (n=103) were selected, based on eligibility criteria, as provided by participant's self-report data (See Chapter 2.2.6).

Except where stated, analysis were conducted within individuals reporting knee pain who underwent further clinical assessment (n=322).

Figure 4-1. Flow chart showing the item selection process across traits.



ESEM, exploratory structural equation modelling; PPT, pressure pain detection threshold.
#Only relevant for items originating from established questionnaires measuring specific traits.

4.4.2. Measures

4.4.2.1. Self-Report measures

Items generated from the initial KPIC item pool (Chapter 3.6) were shortlisted for further analysis in the present chapter. Each of the traits shortlisted following ESEM and content validity analyses in Chapter 3, are listed below:

1. Neuropathic like pain;
2. Intermittent Pain;
3. Constant Pain;
4. Catastrophic thinking;
5. Anxiety;
6. Depression;
7. Fatigue;
8. Cognitive Impact; and
9. Pain distribution.

Rasch-transformed questionnaire scores were used when previously validated in knee pain cases (painDETECT, ICOAP) (Moreton et al., 2015; Moreton, Wheeler, Walsh, & Lincoln, 2012), otherwise non-transformed scores were used (HADS, PCS). Items were coded so that higher scores represented greater pain or distress.

For the current study, pain distribution was captured using areas shaded by the participant on a body manikin. Based on the original 45-site manikin coding employed within the KPIC baseline survey (Appendix 2.1., *p273*), revised manikin coding approaches were derived. Thus, to generate a continuous measure for the number of sites recorded as painful by respondents, the number of sites on the manikin were collapsed into 7-and 23-topographical areas (Appendix 2.2*, p274* and Appendix 2.3, *p274*). To also generate a binary classification measure for pain distribution, painful sites on the manikin were further categorized according to the following criteria:

Knee pain and plus presence of (i) American College of Rheumatology Widespread Pain (ACR's WSP) criteria (Wolfe et al., 1990); (i) pain contralateral to the index knee; (ii) other painful sites above the waist; (iii) other painful sites below the waist; or (iv) other painful sites located axially – Appendix 2.4 to 2.8 (*p275 to p277*). The 2 continuous- and 5 binary-approaches to quantifying pain distribution were assessed to identify the optimum classification criteria for central mechanisms using the body pain manikin.

4.4.2.2. Pressure Pain Detection Thresholds

Details of PPT assessment are described within the Methods chapter (Chapter 2.2.6.1). Satisfactory reliability was found for the PPT scores (Intra-rater Concordance Correlation Coefficient, CCC range = 0.51 to 0.86; Inter-rater CCC range = 0.39 to 0.90) (Akin-Akinyosoye et al., 2018). Raw PPT values were not normally distributed, thus PPTs were logarithmically transformed before statistical analysis to achieve normality of the data, and normality confirmed using the Shapiro-Wilk test (Appendix 10, *p354* to *p357*). Primarily, this chapter focuses on PPTs at the primary site, the proximal tibia which is distal to the most painful knee, and a PPT index for central sensitization (Lluch et al., 2014). Findings utilizing PPT scores at other measured anatomical sites were reproduced in secondary analysis.

4.5. Statistical Analysis

Associations between PPT and self-report data in participants with knee pain (n=322) are presented as Spearman's correlation coefficients (r) or standardized regression coefficients (β) from linear regression models. Adjusted p values were obtained using Bonferroni correction. Except where stated, all analyses were conducted within the participant group that reported knee pain and who had undergone PPT assessment (n=322). Demographics are presented as mean (SD) or median (Interquartile Range). Between-group comparisons used Student's t test and, where appropriate, 95% Confidence Intervals (CIs) are presented.

Analyses of the KPIC data in this chapter begins with defining a binary cut-off score for painful sites reported by individuals with knee OA pain. The associations between the QST index of central knee OA pain mechanisms, and the pain distribution trait measured by the manikin, are also assessed.

Subsequently, in order to select items for inclusion within the developing questionnaire, item selection criteria (Figure 4-1). Each of the criteria are discussed in detail below. Following item selection, CFA procedures were employed to assess the construct validity of the selected items. Thus, this chapter closes by assessing whether or not the selected items were all measuring one underlying latent trait. Further details on the methodology applied to across each of the study objectives are provided below:

4.5.1. Manikin Quantification

Standardized z-scores for log-transformed QST measurements were calculated for individual patients with knee pain using Equation 4.

Equation 4 Z-score.

$$Z\ score = \frac{Participant\ Value - Mean\ value\ for\ control\ group}{SD\ for\ control\ group}$$

PPT values below the 10th percentile (Z-scores >1.28) for the overall population (n=420) were classified as abnormally increased sensitivity (gain-of-function) at the measured site (Coronado et al., 2014), and represents absolute abnormalities within the affected individuals. PPT values served as a reference test during ROC analysis to identify the number of painful sites other

than the knee, reported on the body pain manikin, that is indicative of central pain mechanisms. Cut-off values for the number of painful sites out of 7 and 25 were selected that maximized sensitivity while maintaining a minimum specificity of 0.75 for predicting PPT gain-of-function (Vetter, Schober, & Mascha, 2018). Associations between PPTs, the ROC-derived and a priori predefined binary classifications of pain distribution, were compared. Where significant relationships were identified, the binary classification of the body pain manikin with the strongest association with PPTs was selected as the optimal classifier of central pain mechanisms.

4.5.2. Item Selection

This study sought to select the best performing item representing each trait shown to reflect central pain mechanisms by comparing performance of the shortlisted items across the sequential criteria provided below.

As illustrated in **Error! Reference source not found.**Figure 4-1, a series of criteria were developed to inform item selection. Items considered for selection in this chapter were previously shown to be one of the 2 highest loading items following ESEM, and showed content validity following expert ratings of each items as measures of central knee OA pain mechanisms. Other criteria assessed in this chapter to aid item selection, are described below:

Item redundancy: Inter-item correlation was assessed using spearman's correlation. Highly correlated items ($r>0.60$) have been suggested to show redundancy (El Miedany, 2016), thus where ($r>0.60$), only one item showing redundancy was considered for inclusion.

Item endorsement: The distribution of responses for each item response category was also assessed. Each shortlisted item was assessed to ensure that there was an even distribution of endorsement frequencies across response categories (Petrillo, Cano, McLeod, & Coon, 2015). Where more than 80% of individuals endorsed 1 category, the item was excluded from item selection.

PPT association: The strength of associations for each item and questionnaire with PPTs were assessed to ensure that selected items were associated with a PPT index of central pain mechanisms. Where there were

no significant associations, items were excluded from further consideration for item selection.

Where more than 1 item met each of the apriori criteria described above, performance across all the item selection criteria, including ESEM item loading values and modified kappa values (*as identified in Chapter 3.6*), item endorsement and strength of associations with PPTs (*as identified in the current chapter*), were compared. Thus, the selected items in this chapter were deemed to be the most representative for each key trait linked to central knee OA pain mechanism.

4.5.3. Validation of selected items

For factor analysis of the selected items, participants with knee pain who had undergone PPT assessment (n=322) were randomly allocated into two equal groups using Stata, version 14.2, in order to avoid spurious or chance effects (Flora & Flake, 2017). ESEM was used with one group and the resulting model was tested in the other group using CFA.

PPT variance explained by the identified factor(s) in fully adjusted models (Adjusted for age, sex and BMI), were compared with the variance explained by the host questionnaires. Chronbach's alpha (α) was employed to determine the internal consistency of the final 8 items.

This study further sought to determine whether traits represented by the host questionnaire explained the associations between PPT and items selected from that questionnaire,. For example, we assessed whether the relationship between the selected item (e.g. the depression item) and PPTs was explained by the derived score for the depression questionnaire (which excludes the score for the selected depression item). Derived questionnaire scores for each host questionnaire were calculated by subtracting 'the score for each selected item' from 'the summary score for the respective host questionnaire'. For example, the derived questionnaire score depression was assessed using the equation below:

Equation 5 Example for obtaining derived questionnaire score

$$\begin{aligned} &Derived\ Depression\ Score \\ &\quad = [HADS\ depression\ subscale\ score] \\ &\quad - [selected\ depression\ item\ score]) \end{aligned}$$

This chapter also assessed whether the association between PPT and any identified latent trait(s), was adjusted for each of the derived questionnaire scores. Should a significant relationship between PPTs and the trait be maintained, it would suggest that the relationship between both self-report and QST measure of CS are independent on the traits measured by the previously existing questionnaires.

Analyses were performed using Stata, version 14.2 (StataCorp, 2015), except that ESEM and CFA used MPlus, version 7.4 (Muthén, 2012).Demographics are presented as mean (SD) or median (Interquartile Range). Between-group comparisons used Student's t test and, where appropriate, 95% Confidence Intervals (CIs) are presented.

4.6. Results

4.6.1. Participants Characteristics

The 322 participants with knee pain were on average 59 (SD 10) years of age, had an average BMI of 29 (SD 7), and most were female (61%). Participants without knee pain (n=98, 60% female, age 60±10 y) displayed geometric mean PPT at the proximal tibia of 383 (95% CI 169 to 780) kPA, similar to those with knee pain (358 (95% CI 134 to 871) kPa, p=0.27).

Participant demographics and clinical characteristics for the knee pain group are summarized within Table 4-1.

4.6.2. Pressure pain detection thresholds

Lower PPTs were associated with female sex (females; 314 (287 to 343) kPa, males; 428 (391 to 473) kPa, p<0.0001) and higher BMI (*r* = -0.19, *P* = 0.002), but not with age (*r* = -0.01, 1 *P* = 0.83).

Table 4-1. Demographics and clinical characteristics of participants with knee pain.

	knee pain sample			p
	Overall (n = 322)	**Exploratory (n = 168)**	**Confirmatory (n = 154)**	
Gender; n (%) female	197 (61%)	99 (59%)	98 (64%)	0.387
Age; mean ± SD years	59.4 ± 9.5	59.9 ± 9.7	59.9 ± 9.8	0.978
BMI; mean ± SD kg/m^2	29.5 ± 6.1	29.3 ±5.6	30.0 ± 6.5	0.301
PPT scores				
Proximal tibia PPT (kPA)	372 (265 – 528)	391 (268 – 523)	361 (249 – 528)	0.961
Sternum PPT (kPA)	276 (260 – 293)	276 (252 – 302)	276 (252 – 302)	0.958
Medial Joint line PPT (kPA)	450 (416 – 483)	450 (403 – 498)	450 (399 – 503)	0.996
Lateral Joint line PPT (kPA)	534 (493 – 572)	534 (483 – 590)	534 (478 – 590)	0.958

Table continued on next page

Data are median (interquartile ranges, IQR) except where indicated, and are given for all 322 cases. Questionnaire data are presented where complete data available (constant-Intermittent and Constant Osteoarthritis Pain questionnaire (ICOAP) n=280; intermittent-ICOAP n=296; Anxiety-Hospital Anxiety and Depression Scale (HADS) n=315; Depression-HADS n=314; Pain Catastrophizing Scale, PCS, n = 314; PainDETECT Questionnaire n=282). P values indicate no significant differences between exploratory and confirmatory subgroups used for item factor analysis.

Table 4-1(Cont.). Demographics and clinical characteristics of participants with knee pain.

	knee pain sample			p
	Overall (n = 322)	**Exploratory (n = 168)**	**Confirmatory (n = 154)**	
Questionnaire Scores				
Constant pain-ICOAP (possible range 0 – 24)	6 (3 – 11)	6 (3 – 11)	6 (3 – 12)	0.748
Intermittent pain-ICOAP (possible range 0 – 22)	8 (5 – 14)	8 (5 – 14)	9 (5 – 14)	0.938
PainDETECT (possible range -1 – 38)	9 (5 – 14)	9 (5 – 14)	9 (5 – 14)	0.562
Pain Catastrophizing Scale (possible range 0 – 52)	8 (3 – 20)	8 (3 – 20)	8 (3 – 19)	0.832
Anxiety-HADS (possible range 0 – 14)	6 (4 – 10)	6 (4 – 9)	7 (4 – 10)	0.094
Depression-HADS (possible range 0 – 14)	5 (3 – 8)	4 (3 – 8)	5 (3 – 8)	0.782

Data are median (interquartile ranges, IQR) except where indicated, and are given for all 322 cases. Questionnaire data are presented where complete data available (constant-Intermittent and Constant Osteoarthritis Pain questionnaire (ICOAP) n=280; intermittent-ICOAP n=296; Anxiety-Hospital Anxiety and Depression Scale (HADS) n=315; Depression-HADS n=314; Pain Catastrophizing Scale, PCS, n = 314; PainDETECT Questionnaire n=282). P values indicate no significant differences between exploratory and confirmatory subgroups used for item factor analysis.

For those with knee pain, PPT was not associated with radiographic OA severity (r = -0.041, p = 0.491), but was associated with a painDETECT measure of knee pain severity ("How would you rate your most painful knee pain on a 0-10 scale at the present time, that is right now") (r=-0.18, p=0.002). Pain severity showed a weak but significant relationship with radiographic OA severity (r = 0.15, p = 0.007).

4.6.3. Manikin Quantification

Of the 322 individuals reporting knee pain, 62 (19%) reported pain in ≥5/7 other painful sites, 86 (27%) reported pain in ≥6/23 painful sites additional to knee.

189 (59%) reported pain above the waist. 169 (52%) reported pain below the waist, 119 (37%) reported pain contralateral to the index knee, 151 (47%) reported pain located axially, and 31 (10%) reported pain according to ACR's criteria for widespread pain. The number of other sites reported as painful in addition to knee pain was negatively correlated with PPT at the proximal tibia distal to the index knee (23 other sites: r =-0.16, p=0.008; 7 other sites: r =-0.16, p=0.007). The area under the curve for the tested continuous scorings of the body pain manikin were poor (7-sites: AUC 95%CI = 0.57 (0.48 – 0.67); 23-sites: AUC 95%CI = 0.58 (0.48 – 0.67).

Cut off points of ≥5/7 or ≥6/23 painful sites additional to knee, optimally predicted low PPT (specificity >0.75, accuracy 73.4%) - Appendix 11.1 (*p358*). `Knee Pain plus other pain below the waist' showed significant association with proximal tibia PPT (β=-0.14; p<0.02), but other a priori defined binary pain distribution categories did not (Table 4-2). ACR widespread pain classification did not significantly predict PPT, whether including (β = -0.03, p=0.55) or excluding (β= -0.05; p=0.37) knees as painful sites. The ROC-derived classifications also showed significant associations with PPTs – (Table 4-2).

Due to ease of application, and because the strength of association between the 'Knee pain plus other pain below the waist' classification, the a priori binary classification of 'Knee pain plus other pain below the waist' was selected for further analyses over the ROC-derived classification criteria.

Table 4-2. Association between PPTs, and binary manikin classifications across 322 individuals with knee pain.

	Proximal Tibia PPTs		
	b (95% CI)	β	p
Roc-Derived Classifications			
≥5/7 other sites	-0.20 (-0.37 to -0.03)	-0.14	0.018
≥6/23 other sites	-0.19 (-0.34 to -0.04)	-0.14	0.015
A priori Classifications			
Above waist	-0.08 (-0.22 to -0.06)	-0.07	0.260
Below waist	**-0.17 (-0.30 to -0.03)**	**-0.14**	**0.016**
Contralateral to index knee	-0.14 (-0.28 to 0.002)	-0.12	0.053
Axial pain	-0.01 (-0.15 to 0.12)	-0.01	0.872
ACR's Widespread pain[a]	-0.08 (-0.34 to 0.18)	-0.03	0.551

[a]Widespread pain; classified according to American College of Rheumatology criteria[37], including knee pain. Bold indicates statistically significant associations. ROC; receiver-operating curve. Log-transformed pressure pain detection thresholds (PPT) at (medial or lateral tibiofemoral joint line (JL), or remote (sternum) from the index knee reported here. Data utilized from knee pain sample (n=322). Unstandardized (b) and standardized (β) regression coefficients are presented. **Rows in bold indicate significant findings (p<0.05).**

4.6.4. Item Selection

Each questionnaire from which items were shortlisted showed significant negative associations at a univariate level with Proximal tibia PPT (β= -0.09 to -0.21, each p<0.05 except intermittent-ICOAP, p=0.13) –Table 4-3.

None of the items selected following expert review items showed response category endorsed by ≥80% of participants. 14 items displayed significant negative associations with PPT (Table 4-4), however, 5 items representing catastrophizing (n=3), neuropathic-like symptoms (n=1) and anxiety (n=1), did not show significant associations with PPTs.

Table 4-3. Association between proximal tibia PPTs and summary scores for questionnaires.

	Unadjusted Model				**Model adjusted for age, sex and BMI**			
Traits	B (95% CI)	S.E (for b)	β	p	B (95% CI)	S.E (for b)	β	p
Anxiety - HADS	**-0.02 (-0.04 to -0.005)**	**0.008**	**-0.16**	**0.008**	-0.01 (-0.03 to 0.0002)	0.008	-0.12	0.05
Depression – HADS	**-0.02 (-0.04 to -0.002)**	**0.009**	**-0.13**	**0.03**	-0.01 (-0.03 to 0.006)	0.009	-0.08	0.2
Catastrophizing - PCS	**-0.006 (-0.01 to -0.001)**	**0.002**	**-0.13**	**0.03**	**-0.005 (-0.01 to -0.0003)**	**0.002**	**-0.13**	**0.04**
Constant Pain – ICOAP[#]	**-0.02 (-0.04 to -0.01)**	**0.007**	**-0.21**	**<0.001**	**-0.02 (-0.03 to -0.003)**	**0.007**	**-0.15**	**0.02**
Intermittent Pain – ICOAP[#]	-0.01 (-0.03 to -0.004)	0.009	-0.09	0.1	-0.006 (-0.02 to 0.01)	0.009	-0.04	0.5
Neuropathic symptoms – PainDETECT[#]	**-0.02 (-0.03 to -0.008)**	**0.007**	**-0.19**	**0.002**	**-0.02 (-0.03 to -0.002)**	**0.007**	**-0.15**	**0.02**
Pain Distribution	**-0.17 (-0.30 to -0.03)**	**0.07**	**-0.14**	**0.02**	-0.13 (-0.3 to 0.01)	0.07	-0.11	0.06

[#] Rasch transformed scores applied for regression analysis

Rows in bold approaching statistical significance (p<0.05)

Table 4-4. Item performance f0or each statistical criteria to select best performing items across traits.

Shortlisted Items (items = 17)[#]	Traits	Questionnaire – ESEM loading score	Expert rating (*k**)	Respondents endorsing scores >0 (%)	Correlation with PPTs (Spearman's rho)
"I look forward with enjoyment to things"	Depression	HADS - Depression (0.94)	0.64	54%	-0.12*
"I still enjoy the things I used to enjoy"	**Depression**	**HADS -Depression (0.83)**	**0.71**	**75%**	**-0.15***
"I can't seem it keep it out of my mind"	Catastrophic thinking	PCS - Rumination (0.92)	0.71	52%	-0.11
"I keep thinking about how much it hurts"	**Catastrophic thinking**	**PCS - Rumination (1.00)**	**0.83**	**59%**	**-0.13***

Table continued on next page

Items in bold represent items selected as "best performing items". *p<0.05.

[#]Items presented (items = 17) were rated by experts to show relevance to centrally augmented mechanisms following expert rating (*k**>0.60).

Items originating from established questionnaires showed the highest significant (p<0.05) associations with each identified latent trait during ESEM analysis.

Domains measured by singular items (item specific domains) not entered into ESEM.

Hospital Anxiety and Depression scale (HADS); Modified PainDETECT Questionnaire (MPDQ); Pain Catastrophizing Scale (PCS), Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire. Fatigue, Pain Distribution and Cognitive Impact measured by singular items

Table 4-4(Cont.). Item performance for each statistical criteria to select best performing items across traits.

Shortlisted Items (items = 17)[#]	Traits	Questionnaire – ESEM loading score	Expert rating (*k**)	Respondents endorsing scores >0 (%)	Correlation with PPTs (Spearman's rho)
"I feel I can't go on"	Catastrophic thinking	PCS - Helplessness (1.00)	0.78	24%	-0.09
"I feel I can't stand it anymore"	Catastrophic thinking	PCS - Helplessness (0.93)	0.78	56%	-0.09
Is cold or heat (bath water) in this area occasionally painful?	**Neuropathic Symptoms**	**MPDQ - Evoked symptoms (0.86)**	**0.73**	**43%**	**-0.23***
Over the past month, in your most painful knee, is light touching (clothing, a blanket) in this area painful?	Neuropathic Symptoms	MPDQ - Evoked symptoms (0.56)	0.79	40%	-0.21*

Table continued on next page

Items in bold represent items selected as "best performing items". *p<0.05.

[#]Items presented (items = 17) were rated by experts to show relevance to centrally augmented mechanisms following expert rating (*k**>0.60).

Items originating from established questionnaires showed the highest significant (p<0.05) associations with each identified latent trait during ESEM analysis.

Domains measured by singular items (item specific domains) not entered into ESEM.

Hospital Anxiety and Depression scale (HADS); Modified PainDETECT Questionnaire (MPDQ); Pain Catastrophizing Scale (PCS), Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire. Fatigue, Pain Distribution and Cognitive Impact measured by singular items.

Table 4-4(Cont.). Item performance for each statistical criteria to select best performing items across traits.

Shortlisted Items (items = 17)[#]	Traits	Questionnaire - ESEM (loading score)	Expert rating (*k**)	Respondents endorsing scores >0 (%)	Correlation with PPTs (Spearman's rho)
In the past week, how much has your knee pain that comes and goes affected your sleep?	Intermittent pain experience	Intermittent ICOAP - (0.94)	0.64	56%	-0.17*
In the past week, how upset or worried have you been by your knee pain that comes and goes?	Intermittent pain experience	Intermittent ICOAP - (0.94)	0.69	71%	-0.14*
In the past week, how much has your constant knee pain affected your sleep?	**Constant pain experience**	**Constant ICOAP - (0.95)**	**0.64**	**68%**	**-0.21***
"I get a sort of frightened feeling as if something awful is about to happen"	Anxiety	HADS -Anxiety (0.83)	0.69	60%	-0.08

Table continued on next page

Items in bold represent items selected as "best performing items". *p<0.05.

[#]Items presented (items = 17) were rated by experts to show relevance to centrally augmented mechanisms following expert rating (*k**>0.60).

Items originating from established questionnaires showed the highest significant (p<0.05) associations with each identified latent trait during ESEM analysis.

Domains measured by singular items (item specific domains) not entered into ESEM.

Hospital Anxiety and Depression scale (HADS); Modified PainDETECT Questionnaire (MPDQ); Pain Catastrophizing Scale (PCS), Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire. Fatigue, Pain Distribution and Cognitive Impact measured by singular items.

Table 4-4(Cont.). Item performance for each statistical criteria to select best performing items across traits.

Shortlisted Items (items = 17)[#]	Traits	Questionnaire - ESEM (loading score)	Expert rating (*k**)	Respondents endorsing scores >0 (%)	Correlation with PPTs (Spearman's rho)
Over the past month, do you have a tingling or prickling sensation in the area of your most painful knee 'pain' (like crawling ants or electrical tingling)?	Neuropathic Symptoms	MPDQ - Spontaneous symptoms (1.00)	0.66	50%	-0.09
"I get sudden feelings of panic"	**Anxiety**	**HADS -Anxiety (0.80)**	**0.61**	**53%**	**-0.19***
Knee pain plus other pain below the waist	**Pain Distribution**	**-**	**0.81**	**52%**	**-0.14***
Does your pain or other bodily symptoms stop you from concentrating on what you are doing?	**Cognitive Impact**	**-**	**0.71**	**74%**	**-0.18***
In the past month, did you feel tired on most days?	**Fatigue**	**-**	**0.61**	**96%**	**-0.15***

Items in bold represent items selected as "best performing items". *p<0.05.
[#]Items presented (items = 17) were rated by experts to show relevance to centrally augmented mechanisms following expert rating (*k**>0.60).
Items originating from established questionnaires showed the highest significant (p<0.05) associations with each identified latent trait during ESEM analysis.
Domains measured by singular items (item specific domains) not entered into ESEM.
Hospital Anxiety and Depression scale (HADS); Modified PainDETECT Questionnaire (MPDQ); Pain Catastrophizing Scale (PCS), Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire. Fatigue, Pain Distribution and Cognitive Impact measured by singular items.

The items shortlisted after expert review all displayed significant positive associations with each other (r range =0.07 to 0.87, Appendix 11.2, *p360*). Intermittent-ICOAP items also showed strong correlations ($r > 0.80$, $p < 0.05$) with corresponding constant ICOAP items. Based on the lack of associations between the intermittent ICOAP subscale and PPTs, and the item redundancy observed with corresponding constant ICOAP items, items originating from the intermittent ICOAP subscale where therefore excluded from the item shortlist.

Table 4-4 shows results for each of the shortlisted items across sequential criteria. Following comparison of performances, a single item which showed best performance across each of the apriori criteria was selected to represent each of 8 remaining traits; fatigue, cognitive impact, pain distribution, anxiety, depression, rumination, evoked neuropathic-like symptoms, and sleep disturbance (*originating from constant subscale of the ICOAP*) Validation of self-report traits

The one-factor model also showed the best fit to data from the Confirmatory group (CFI = 0.94; TLI = 0.92; RMSEA = 0.07; WRMR = 0.5; $X^2(df) = 43(20)$). Competing 2- and 3- factor models for these items were not identified in the exploratory group, supporting the one-factor model. Each item was significantly associated with the single latent trait, interpreted as representing central mechanisms of knee pain (Table 4-5). The identified latent trait also predicted knee pain severity measured by the pain intensity item “How would you rate your most painful knee pain on a 0-10 scale at the present time, that is right now” ($\beta = 0.66$; S.E. = 0.05, $p<0.001$), but not radiographic OA severity ($\beta=0.10$; SE=0.07; $p=0.160$)..

The relationship between the latent trait and PPT remained significant even when radiographic OA severity, or pain severity, were accounted for within the model ($\beta=-0.267$; SE=0.07; $p<0.001$, and $\beta=-0.213$; SE=0.06; $p<0.001$, respectively). The 8 selected items displayed a Cronbach’s alpha (α) of 0.80. The latent trait was associated with PPT ($\beta=-0.27$; S.E = 0.07; $p<0.001$), independent of each questionnaire from which items were derived (Table 4-6).

Significant proportion of variation in PPT was explained by each questionnaire alone (R^2 values = 0.10 to 0.13, $p<0.05$). The latent trait also explained a higher proportion of PPT variance ($R^2 = 0.17$, $p<0.05$), compared to that

explained by any host questionnaire (R^2 values = 0.10 to 0.13, p<0.05). Associations between each selected item and PPT were reduced and lacked significance after adjusting for derived host questionnaire scores (Table 4-7), except for the neuropathic item on cold or heat on the area causing pain (β= -0.21, p <0.05) and the anxiety item “I get sudden feelings of panic” (β= -0.19, p <0.05), where the relationship remained significant after adjusting for derived host questionnaire scores.

Table 4-5. Standardized item loadings for the 8 selected items in a single factor model in exploratory and confirmatory subgroups.

Item	Trait	Exploratory sample (n=166)	Confirmatory sample (n=154)
"I get sudden feelings of panic"	Anxiety	0.53*	0.49*
"I still enjoy the things I used to enjoy"	Depression	0.57*	0.52*
“Over the past month, in your most painful knee, is cold or heat (bath water) in this area occasionally painful?”	Neuropathic symptoms	0.52*	0.57*
“In the past month, did you feel tired on most days?”	Fatigue	0.62*	0.61*
“Does your pain or other bodily symptoms stop you from concentrating on what you are doing?”	Cognitive Impact	0.79*	0.81*
“Knee pain plus other pain below waist”	Pain distribution	0.44*	0.40*
"I keep thinking about how much it hurts"	Catastrophizing	0.57*	0.58*
“In the past week, how much has your constant knee pain affected your sleep?”	Sleep	0.66*	0.69*

*p<0.05

Table 4-6. Association between latent 'Central mechanisms' trait and Proximal Tibia PPTs.

	Proximal Tibia PPTs		
	β	S.E	P
Unadjusted Model	**-0.27**	**0.07**	**<0.001**
Adjusted for			
Constant Pain experience - ICOAP	**-0.19**	**0.07**	**0.01**
Neuropathic- like pain - PainDETECT	**-0.21**	**0.07**	**0.01**
Catastrophizing - PCS	**-0.28**	**0.08**	**<0.001**
Anxiety - HADS	**-0.24**	**0.07**	**0.001**
Depression - HADS	**-0.26**	**0.08**	**0.001**

The single latent trait identified through the 8 selected items, interpreted as `central mechanisms of knee pain', was associated with pressure pain detection thresholds (PPT) in an unadjusted model, and in models where total scores derived from each of the originating questionnaires (questionnaire summary score minus selected item) were adjusted for.
Standardized regression coefficients (β) presented.

Findings reported here for proximal tibia PPTs were reproduced in secondary analysis utilizing PPT scores at other measured anatomical sites (Appendix 11.3, *p364* and 11.4, *p366*).

4.7. Results Summary

Individuals reporting 'pain other than knee pain below the waist' on the manikin show reduced PPTs at sites distal to the index joint, possibly indicative of centrally augmented pain processing or central sensitization.8 self-report items, representing key traits of anxiety, depression, catastrophizing, neuropathic-like pain, fatigue, sleep disturbance, pain distribution and cognitive impact, were selected for inclusion within the developing questionnaire. These items displayed external validity by significantly contributing to one underlying latent trait, termed 'Central Mechanisms'. This latent trait showed significant association with high pain sensitivity (low PPT) at a site distal to the index knee, indicative of centrally augmented pain. In addition, an optimal binary classification for the assessing pain distribution on the body pain manikin was developed.

Table 4-7. Associations between selected items and proximal tibia PPTs are dependent on traits measured by their host questionnaires.

	Unadjusted model			**Adjusted model**		
Traits	b (95% CI)	β	p	b (95% CI)	β	p
Constant Pain Experience: “In the past week, how much has your constant knee pain affected your sleep?”	-0.11 (-0.17 to -0.04)	-0.21	0.001	-0.08 (-0.17 to 0.02)	-0.15	0.119
Neuropathic- like pain: “Over the past month, in your most painful knee, is cold or heat (bath water) in this area occasionally painful?”	**-0.10 (-0.17 to -0.05)**	**-0.23**	**<0.001**	**-0.10 (-0.17 to -0.03)**	**-0.21**	**0.008**
Catastrophizing: "I keep thinking about how much it hurts"	-0.06 (-0.12 to -0.01)	-0.13	0.03	0.004 (-0.12 to 0.12)	0.007	0.953
Anxiety: "I get sudden feelings of panic"	**-0.13 (-0.21 to -0.05)**	**-0.19**	**0.001**	**-0.12 (-0.24 to -0.01)**	**-0.19**	**0.032**
Depression: "I still enjoy the things I used to enjoy"	-0.10 (-0.18 to -0.02)	-0.15	0.01	-0.06 (-0.16 to 0.04)	-0.09	0.252

In order to explore whether observed univariate associations between each selected item and proximal tibia log-PPTs might be explained by the trait measured by the host questionnaire from the host questionnaire from which it originated, each univariate association was adjusted for the derived host questionnaire score (questionnaire summary score minus selected item). Data are from participants with knee pain sample (n=322).
Bold indicates significant associations after adjustment.
Unstandardized (b) and standardized coefficients (β) are presented.

5. PREDICTIVE VALIDITY: BASELINE SELF-REPORT 'CENTRAL MECHANISMS' TRAIT AS A PREDICTOR OF PERSISTENT KNEE PAIN

5.1. Outline

This chapter reports the relationship between selected items that represent traits associated with central mechanisms of knee OA pain, and future pain outcomes in the KPIC cohort. The ability for the Central Mechanisms trait to discriminate between individuals whose pain persist or resolve over time was assessed in order to investigate the prognosis performance of the self-report trait intended to be measured within the developing tool.

The strength of association between future pain outcomes and self-report traits, other clinical characteristics, and PPTs, were also sought and compared.

5.2. Introduction

QST modalities such as PPTs, and imaging- (e.g., fMRI) provide methods for assessing central mechanisms of knee pain (Gwilym et al., 2009). Low PPT scores distal to the affected joint in people with OA have been associated with central sensitization (Graven-Nielsen & Arendt-Nielsen, 2002). However, employing PPT or brain imaging would be resource-intensive during normal clinical encounters. Thus, there is need for a clinically feasible screening tool that identifies contributions to knee pain from the central nervous system. Such a screening tool might inform mechanism-based treatment for individuals with knee pain (Conaghan, Kloppenburg, Schett, & Bijlsma, 2014). Self-report traits of anxiety, depression, catastrophizing, neuropathic-like pain, fatigue, sleep disturbance, pain distribution, and cognitive impact each is associated with pain intensity and phenotypic markers for central pain mechanisms in individuals reporting knee pain (Ali et al., 2017; Blackburn, Qureshi, Amirfeyz, & Bannister, 2012; Campbell et al., 2015; Dave et al., 2017; Finan et al., 2013; Harden et al., 2003; Hochman et al., 2013; Hodges et al., 2016; Kurien et al., 2016; Lluch et al., 2017; Lluch et al., 2014; Lluch Girbes et al., 2016; Noiseux et al., 2014; Somers et al., 2009; Wylde et al., 2017; Wylde et al., 2015).

The previous chapter (Chapter 4) demonstrated that 8 self-report items, each measuring one of these traits, contribute to a single latent 'Central

Mechanisms' trait. This Central Mechanisms trait was associated with PPTs at a distal site in individuals with knee pain, an index of CS (Graven-Nielsen & Arendt-Nielsen, 2002).

Knee pain might either resolve or persist over time. Knee pain persistence after therapeutic intervention is weakly predicted by structural factors within the knee, including radiographic OA severity and ultrasound effusion (Maricar et al., 2017). Other characteristics have also been found to predict worse pain at follow up, particularly after surgical intervention. These include high BMI (Jacobs, Vranceanu, Thompson, & Lattermann, 2018), longer duration of pain (Van Der Waal et al., 2005), PPT, and self-report traits (Lewis et al., 2015). However, possible associations of central mechanisms with knee pain prognosis in non-surgical contexts have been less thoroughly explored (Van Der Waal et al., 2005). In comparison to these different demographic and disease specific predictors, self-report measures of central mechanisms might more accurately predict how knee pain might change over time across individuals. Thus, measurement of the Central Mechanisms trait might help to improve knee pain prognosis by identifying individuals who might benefit from interventions aiming to reduce CS.

The current study hypothesized that: (i) baseline scores for a self-report Central Mechanisms trait predict worse pain outcomes (pain persistence or persistent pain severity) at 1-year follow-up in people with knee pain more strongly than any single component characteristic, and; (ii) the prognostic performance of the Central Mechanisms trait is superior to predictors of unfavourable pain prognosis such as radiographic evidence of OA pathology (Jacobs et al., 2018; Lewis et al., 2015; Petersen et al., 2015; Petersen et al., 2016; Van Der Waal et al., 2005).

5.3. Aims and Objectives

5.3.1. Aims

By utilizing data from the KPIC cohort at baseline and follow up, this study aims to investigate the ability of a self-report measure of 'central mechanisms' to predict 1-year pain outcomes.

5.3.2. Objectives

1. Investigate and compare the prediction of pain outcomes by baseline measures for (a) central mechanisms trait, (b) PPTs and (c) component questionnaires or indicator items measuring traits that are represented by items measuring the central mechanisms trait.
2. Determine the prognostic characteristics of the central mechanisms trait, compared to other clinical characteristics, such as radiographic OA severity.

5.4. Methods

5.4.1. Participants

The KPIC survey at baseline and at year 1 follow-up, assessed various pain related traits in individuals aged 40 years and over – see Chapter 2.2.5. Out of 2512 participants reporting current knee pain at baseline, 1471 responded to the KPIC survey at 1-year follow-up. A subset of participants reporting knee pain (n=204) who underwent PPT and radiographic assessments at baseline, also responded at year 1 follow-up (See Figure 2-1 for illustrations of KPIC participant recruitment at baseline and 1 year follow-up).

Recruitment was based on procedures described within Chapter 2.2.6.

5.4.2. Measures

A list of the self-report and clinical measures included in this study are provided in Table 5-1. Details of each are provided below:

5.4.2.1. Self-Report measures

Primary outcome measure: Persistence or resolution of knee pain over the past year was determined by response to the question: “In the past 12 months, have you had any pain in or around a knee on most days for at least a month?” (McAlindon, Snow, Cooper, & Dieppe, 1992; O’Reilly, Jones, Muir, & Doherty, 1998). Participants reporting knee pain indicated the affected knee if unilateral, or the worst affected knee if bilateral. Individuals reporting knee pain at baseline, but no knee pain at follow-up, were classified as a ‘resolved pain’ group, and those reporting knee pain at follow-up were classified as a ‘pain persistence’ group.

Table 5-1 List of study measures

Variables	Self-report measure
Primary outcome	Pain Persistence
Secondary outcome	Change in Pain Severity
Primary predictor	Baseline score for Central Mechanisms trait
Secondary predictor	Baseline score for Neuropathic-like symptoms
Secondary predictor	Baseline score for Pain Catastrophizing
Secondary predictor	Baseline score for Anxiety
Secondary predictor	Baseline score for Depression
Secondary predictor	Baseline PPT scores
Secondary predictor	Baseline radiographic OA

Secondary outcome measure: Knee pain severity, reported by individuals with pain at each time point, was determined by response to the 11- point numerical rating scale (NRS) question: “In the past month, how intense was your ‘worst knee pain’ rated on a 0-10 scale, where 0 is ‘no pain’ and 10 is ‘pain as bad as could be’? (Hochman et al., 2011).

Primary baseline predictor: The Central Mechanisms trait score was derived from 8 items representative of the individual component self-report traits measuring anxiety, catastrophizing, cognitive impact, depression, fatigue, neuropathic-like pain, pain distribution and sleep (Chapter 4.6.4). Reverse worded items were coded so that higher scores represented greater pain or distress. Raw scores were linearly transformed to achieve a possible score range for each item of 0 to 3. Pain distribution classified as “pain below the waist additional to knee pain” was captured using areas shaded by the participant on a body manikin (Chapter 4.6.3). For each participant, a summary score for the Central Mechanisms trait (out of 24) was derived by summating transformed scores from each of the 8 self-report items.

Other self-report predictors: The KPIC survey at both baseline and follow-up included established self-report questionnaires for neuropathic-like pain (modified painDETECT questionnaire) (Hochman et al., 2011), ICOAP (Hawker et al., 2008), catastrophic thinking (PCS) (Sullivan et al., 1995), and anxiety and depression (HADS) (Zigmond & Snaith, 1983). Traits of fatigue, cognitive impact (Ferguson & Daniel, 1995) and pain distribution (Lacey et al., 2005), were each measured by single items. Rasch transformed questionnaire scores were used when previously validated in knee pain cases (painDETECT and ICOAP) (Moreton et al., 2015; Moreton et al., 2012), otherwise, original published protocols for questionnaires were followed.

Clinical predictors: PPT and radiographic assessment were measured as described within the KPIC study (Chapter 2.2.6). Satisfactory reliability was found for the PPT scores (Intra-rater Concordance Correlation Coefficient, CCC range = 0.51 to 0.86; Inter-rater CCC range = 0.39 to 0.90) and radiographic severity scores (Intra-rater Weighted Kappa, Kw range = 0.66 to 0.90; Inter-rater Kw, range = 0.65 to 0.93) (Akin-Akinyosoye et al., 2019; Akin-Akinyosoye et al., 2018).

Logarithmically transformed PPT scores and ordinal radiographic severity scores were employed during statistical analysis.

5.5. Statistical Analysis

Except where mPlus was employed to derive factor scores for the Central Mechanisms trait (Muthén, 2012), analyses were performed using Stata, version 14.2 (StataCorp, 2015). Between-group comparisons used student t-test and, where appropriate, 95% CIs are presented. Demographics are presented as mean (SD) or median (Interquartile Range).

5.5.1. Central Mechanisms trait at baseline as a predictor of pain outcomes at 1 year follow-up

Firstly, this study sought to investigate whether the Central Mechanisms trait predicts knee pain persistence, in comparison to other self-report and QST measures. Binary outcomes are most commonly employed for prognostic research questions. The logistic regression model is the most widely used statistical technique for such binary outcomes.

Across all study participants, due to the binary nature of the primary outcome variable (pain persistence/resolution), logistic regression models were employed to assess and compare relationships between baseline scores for self-report measures the pain outcome. Logistic regression analysis, which estimates odds ratios, is often used to adjust for co-variables in cohort studies and randomized controlled trials (RCTs) that study a dichotomous outcome. To avoid any misinterpretation of odds ratios, adjusted risk ratios should be calculated and presented in cohort studies and RCTs (Greenland & Thomas, 1982; Greenland, Thomas, & Morgenstern, 1986; Knol, Vandenbroucke, Scott, & Egger, 2008; Miettinen, 1976). Thus, in this study, the Stata "oddsrisk" command was used to convert odds ratios to risk ratios (RR) with associated confidence intervals (Hilbe, 2008).

Next, this study sought to investigate whether the Central Mechanisms trait predicts change in severity knee pain persistence between baseline and year-1 follow up. Where pain persistence was reported by participants, persistent pain severity (residualized pain severity change scores) served as the secondary pain outcome. Residualized change score (RCS) adjusts the portion of change in pain between baseline and 1 year follow-up that could have been predicted linearly from the baseline scores (Campbell & Kenny, 1999; Cronbach & Furby, 1970). RCS was derived from the formula highlighted in Equation 6 below, where Y= Pain score for individual at follow-up; MY = Mean score for knee pain group at follow-up; X = Pain score for individual at baseline; MX = Mean score for knee pain group at baseline; b = Regression coefficient for regressing Y onto X.

Equation 6 Residualized Change Score.

$$RCS = (Y - MY) - b(X - MX)$$

Unlike ordinary logistic regression, continuous outcomes such as pain intensity typically employ the ordinary least square model ("linear regression") as the reference statistical model. Associations between RCS for knee pain severity serving as the dependent variable, and baseline scores serving as the independent variable, were tested using linear regression models.

Associations for linear regression models are presented as standardized regression coefficients (β). R^2 are reported to demonstrate how much variation

in pain severity was explained by the self-report and clinical traits, in unadjusted models, and in models adjusted for demographic characteristics, radiographic OA severity and symptom duration.

Estimates are presented from crude models, and from fully adjusted models which accounted for other predictors shown in previous studies to be associated with knee pain persistence (including age, sex, BMI, radiographic OA severity, and symptom duration) (Arden et al., 2008; Calvet et al., 2018; Maricar, Callaghan, Felson, & O'neill, 2012; Maricar et al., 2017; Peters, Sanders, Dieppe, & Donovan, 2005). Spearman (r) and eta (η) correlation coefficients for univariate associations are also presented.

Factor-derived scores, following Confirmatory Factor Analyses of the 8 selected items, were also employed within relevant secondary analyses in this study.

Where both knees were measured during clinical assessment (radiographic and PPT assessment), scores from the index knee were employed.

5.5.2. Prognostic Characteristics of the Central Mechanisms trait

Finally, this study sought to demonstrate the prognostic performance of the Central Mechanisms trait, compared to other baseline predictors. The diagnostic performance of a test is the accuracy of a test to discriminate diseased cases from normal controls. ROC curves can also be used to compare the diagnostic performance of two or more tests. Thus, the performance of the Central Mechanisms trait and other baseline predictors in discriminating between pain persistence cases and resolved pain cases was assessed using ROC curves. Univariate logistic regression models were used to estimate and compare the AUC for the self-report Central Mechanisms trait, as well as for other predictors (Cleves & Rock, 2002).

Further ROC analyses sought to establish incremental validity (as described by Chapter 2.3.4.2), by assessing whether the Central Mechanisms trait contributed significantly to univariate models for other predictors of pain persistence (Hosmer Jr et al., 2013; Seshan et al., 2013). To test for incremental validity, the Central Mechanisms trait score was entered sequentially into logistic regression models for each predictor.

5.6. Results

5.6.1. Participant Characteristics

The study population comprised KPIC participants with knee pain at baseline who responded to 1-year follow-up (n=1471, mean (SD) age = 62 (10) years, BMI=28.9 (6.0) kg/m^2, 60% female). As expected because of their selection criteria, participants who underwent radiographic and PPT assessment (n=204) were slightly younger and reported having had knee pain for a shorter duration, but otherwise did not significantly differ from the total study population (Table 5-2).

Across all participants with knee pain at baseline (n=1471), higher baseline Central Mechanisms trait scores were associated longer symptom duration (r=0.14, p<0.0001, older age (r=-0.12, p<0.0001), female sex (η = 0.30, p<0.001) and higher BMI (r=0.27, p<0.0001) - Appendix 12.1, *p367*. In those who underwent radiographic and PPT assessment (n=204), higher baseline Central Mechanisms trait scores were associated with lower PPT at each anatomical site (range r=-0.21 to -0.37, p<0.05) and with radiographic OA severity (r = 0.15, p=0.034) – Appendix 12.1 (*p367*).

Normal distribution was demonstrated for the summary score for the baseline Central Mechanisms trait (n=250), and the residualized change score for the pain intensity outcome measure (Appendix 16, p409).

5.6.2. Prediction of knee pain persistence

Knee pain persistence at 1 year was reported by 976 (66%) participants, of whom 133 had radiographic and PPT assessments at baseline. Compared to participants reporting pain resolution at 1-year follow-up (n=476), those with pain persistence (n=976) had significantly higher baseline self-report Central Mechanisms trait score, longer symptom duration and higher BMI (Table 5-3).

Associations between Central Mechanisms trait and pain persistence were also demonstrated in the subgroup of participants who underwent radiographic and PPT assessment (n=204, RR=2.14, 95%C.I. 1.49,3.08, p=0.001).

Table 5-2. Participant characteristics at baseline.

Participant Characteristics	Total knee pain sample (n = 1471)	Radiographic and PPT assessed subgroup (n=204)	P
n (%) female	876 (60%)	124 (61%)	0.776
Age; mean ± SD years	62 ± 10	61 ± 10	0.018
BMI; mean ± SD kg/m^2	28.9 ± 6.0	29.5 ± 5.8	0.148
Self-report scores			
Central Mechanisms (possible range 0 – 24)	8 (5 – 11)	8 (5 – 11)	0.539
Modified painDETECT (possible range -1 – 38)	12 (9 – 14)	11 (9 – 15)	0.698
Pain Catastrophising Scale (possible range 0 – 52)	8 (3 – 19)	8 (3 – 21)	0.454
Anxiety-HADS (possible range 0 – 14)	7 (4 – 10)	6 (4 – 10)	0.279

Table continued on next page

Rows in bold indicate significant associations (p<0.05). PPT = Pressure Pain Detection Thresholds

* Measured by single items. + Pain Distribution measured on the body pain manikin is coded as present when individual reports knee pain plus, other pain below the waist.

Data are median (interquartile ranges [IQRs]) except where indicated. Geometric values for log-transformed PPTs are given for all 204 cases. Questionnaire data are presented where complete data available for questionnaire (Constant-Intermittent and Constant Osteoarthritis Pain scale [ICOAP] n = 1354; intermittent-ICOAP n = 1319; Anxiety-Hospital Anxiety and Depression scale [HADS] n = 1431; Depression-HADS n = 1439; Pain Catastrophizing Scale [PCS], n = 1409; Modified PainDETECT Questionnaire n = 1155 and Central Mechanisms trait score n=1300).

Table 5-2(Cont.). Participant characteristics at baseline.

Participant Characteristics	Total knee pain sample (n = 1471)	Radiographic and PPT assessed subgroup (n=204)	P
Depression-HADS (possible range 0 – 14)	5 (3 – 8)	4 (3 – 7)	0.087
Cognitive Impact*(possible range 0 – 4)	2 (0 – 2)	2 (0 – 2)	0.429
Pain Distribution+* n (%)	791 (54%)	109 (53%)	0.916
Fatigue*(possible range 0 – 4)	2 (2 – 3)	2 (2 – 3)	0.999
Sleep*(possible range 0 – 4)	1 (0 – 2)	1 (0 – 2)	0.624
Pain in the past month* (possible range 0 – 10)	4 (2 – 7)	4 (2 – 7)	0.891
Symptom duration; years	**10 (4 – 20)**	**2 (1 – 3)**	**<0.0001**

Table continued on next page

Rows in bold indicate significant associations (p<0.05). PPT = Pressure Pain Detection Thresholds

* Measured by single items. + Pain Distribution measured on the body pain manikin is coded as present when individual reports knee pain plus, other pain below the waist.

Data are median (interquartile ranges [IQRs]) except where indicated. Questionnaire data are presented where complete data available for questionnaire (Constant-Intermittent and Constant Osteoarthritis Pain scale [ICOAP] n = 1354; intermittent-ICOAP n = 1319; Anxiety-Hospital Anxiety and Depression scale [HADS] n = 1431; Depression-HADS n = 1439; Pain Catastrophizing Scale [PCS], n = 1409; Modified PainDETECT Questionnaire n = 1155 and Central Mechanisms trait score n=1300).).

Table 5-2(Cont.). Participant characteristics at baseline.

Participant Characteristics	Total knee pain sample (n = 1471)	Radiographic and PPT assessed subgroup (n=204)	P
Radiographic and PPT scores			
Radiographic OA (KL scores≥1); n (%)	-	108 (53%)	-
Proximal tibia PPT (kPa)	-	528 (420 – 678)	-
Sternum PPT (KPa)	-	358 (268 – 450)	-
Medial Joint Line (KPa)	-	508 (327 – 692)	-
Lateral Joint Line (KPa)	-	1261 (1043 – 1451)	-

PPT = Pressure Pain Detection Thresholds
* Measured by single items.
+ Pain Distribution measured on the body pain manikin is coded as present when individual reports knee pain plus, other pain below the waist.
Data are median (interquartile ranges [IQRs]) except where indicated. Geometric values for log-transformed PPTs are given for all 204 cases.
Questionnaire data are presented where complete data available for questionnaire (Constant-Intermittent and Constant Osteoarthritis Pain scale [ICOAP] n = 1354; intermittent-ICOAP n = 1319; Anxiety-Hospital Anxiety and Depression scale [HADS] n = 1431; Depression-HADS n = 1439; Pain Catastrophizing Scale [PCS], n = 1409; Modified PainDETECT Questionnaire n = 1155 and Central Mechanisms trait score n=1300).

Table 5-3. Participant baseline characteristics compared between pain persistence and pain resolution groups.

Participant Characteristics	Resolved pain	Pain persistence	p
Female; n (%)	277 (58%)	591 (61%)	0.402
Age; mean ± SD years	62 ± 10	62 ± 10	0.643
BMI; mean ± SD kg/m^2	**28.0 ± 5.3**	**29.4 (6.3)**	**0.0001**
Questionnaire Scores	(n=476)	(n=976)	
Central mechanisms (possible range 0 – 24)	**6 (4 – 10)**	**9 (5 – 11)**	**<0.0001**
Modified painDETECT (possible range -1 – 38)	**4 (2 – 9)**	**10 (5 – 16)**	**<0.0001**
Pain Catastrophizing Scale (possible range 0 – 52)	**5 (2 – 13)**	**10 (4 – 22)**	**<0.0001**
Anxiety-HADS (possible range 0 – 14)	**6 (3 – 9)**	**7 (4 – 11)**	**<0.0001**

Table continued on next page

Rows in bold indicate significant associations (p<0.05)

Baseline characteristics data are median (interquartile ranges [IQRs]) except where indicated

* Measured by single items ⁺ Pain Distribution measured on the body pain manikin was coded as present when individual reported knee pain plus other pain below the waist.

Table 5-3(Cont.). Participant baseline characteristics compared between pain persistence and pain resolution groups.

Participant Characteristics	Resolved pain	Pain persistence	p
Depression-HADS (possible range 0 – 14)	**4 (2 – 7)**	**5 (3 – 8)**	**<0.0001**
Cognitive Impact* (possible range 0 – 4)	**1 (0 – 2)**	**2 (1 – 2)**	**<0.001**
Pain Distribution⁺* n (%)	**0 (0 – 1)**	**1 (0 – 1)**	**<0.001**
Fatigue*(possible range 0 – 4)	**2 (2 – 3)**	**2(2 – 3)**	**<0.001**
Sleep*(possible range 0 – 4)	**0 (0 – 1)**	**1 (0 – 2)**	**<0.001**
Symptom duration*#; years (possible range 0 – 79)	**7 (2 – 17)**	**11 (5 – 22)**	**0.013**

Table continued on next page

Rows in bold indicate significant associations (p<0.05) Baseline characteristics data are median (interquartile ranges [IQRs]) except where indicated

* Measured by single items ⁺ Pain Distribution measured on the body pain manikin was coded as present when individual reported knee pain plus other pain below the waist.

Table 5-3(Cont.). Participant baseline characteristics compared between pain persistence and pain resolution groups.

Participant Characteristics	Resolved pain	Pain persistence	p
PPT and radiographic scores	(n=85)	(n=118)	
Proximal tibia PPT (kPa)	561 (518 – 609)	513 (473 – 555)	0.123
Sternum PPT (KPa)	365 (337 – 399)	337 (308 – 369)	0.214
Medial Joint Line (KPa)	**523 (469 – 589)**	**407 (358 – 469)**	**0.008**
Lateral Joint Line (KPa)	**1299 (1236 – 1380)**	**1188 (1130 – 1249)**	**0.015**
Radiographic OA (KL scores≥1) ; n (%)	59(83%)	96 (84%)	0.123

Rows in bold indicate significant associations (p<0.05)
Baseline characteristics data are median (interquartile ranges [IQRs]) except where indicated
Geometric values of pressure pain detection thresholds (PPTs) are presented.
* Measured by single items ⁺ Pain Distribution measured on the body pain manikin was coded as present when individual reported knee pain plus other pain below the waist.

In this subgroup (n=204), pain persistence was also associated with lower baseline PPT at the medial joint line (RR=-0.65, 95%C.I. 0.47, 0.89, p=0.009) and lateral joint line (RR=-0.68, 95%C.I. 0.49, 0.93, p=0.017) of the index knee, and with the presence of radiographic OA severity (RR=1.69, 95%C.I. 1.40, 1.85 p=0.001)(Table 5-4).

Prediction of pain persistence by Central Mechanisms trait score remained significant after adjustment for age, sex, BMI, radiographic OA severity, and symptom duration (RR=2.10, 95%C.I. 1.36, 3.25, p=0.001, Table 5-5). Self-report traits of neuropathic-like symptoms, catastrophizing, anxiety, depression, cognitive impact and pain distribution also significantly predicted knee pain persistence in models adjusted for demographic variables, radiographic OA severity and symptom duration (range RR=1.58 to 2.17, p<0.02, Table 5-5). Baseline PPTs did not significantly predict pain persistence after adjustment for demographic variables, radiographic OA severity and symptom duration (range RR=0.78 to 0.99, p>0.25, Table 5-5).

5.6.3. Prediction of persistent pain severity

Individuals with knee pain persistence (n=976) rated their persistent knee pain severity in the past month at 1 year follow up as median 6 (IQR 4 to 8, possible range 0 – 10). Higher baseline Central Mechanisms trait scores were associated with higher residualized change scores for increasing pain severity in people with persistent knee pain (n=1471, β=0.47, 95%C.I. 0.42,0.53, p<0.001, Table 5-4). Associations between baseline Central Mechanisms trait and increasing pain severity in people with persistent knee pain were also demonstrated in the subgroup of participants who underwent radiographic and PPT assessment (n=133, β=0.58, 95%C.I. 0.39,0.76, p<0.001). In this subgroup, residualized change score for increasing persistent knee pain severity also was positively associated with lower baseline PPT at the medial joint line (β =-0.27, 95%C.I. -0.46, -0.07, p=0.009) and lateral joint line (β =-0.27, 95%C.I. -0.50, -0.08, p=0.003) of the index knee, although association with radiographic OA severity did not reach statistical significance (β =0.18, 95%C.I. -0.03, 0.36 p=0.054) (Table 5-4).

Table 5-4. Prediction of pain persistence and persistent pain severity at year 1 follow up by baseline self-report traits and PPT in unadjusted models.

	Pain persistence at year 1		**Persistent pain severity**		
Traits	RR (95% CI)	p	β (95% CI)	R^2	p
Female; n (%)	**1.05 (0.94, 1.17)**	**0.402**	**0.06 (0.001, 0.13)**	**0.003**	**0.048**
Age; mean ± SD years	1.03 (0.92, 1.14)	0.643	0.01 (-0.06, 0.07)	<0.001	0.830
BMI; mean ± SD kg/m^2	**1.29 (1.14, 1.46)**	**<0.001**	**0.18 (0.11, 0.24)**	**0.03**	**<0.001**
Questionnaire Scores	(n=1471)		(n=976)		
Central mechanisms (possible range 0 – 24)	**1.73 (1.52, 1.98)**	**<0.001**	**0.47 (0.42, 0.53)**	**0.25**	**<0.001**
Modified painDETECT (possible range -1 – 38)	**2.32 (1.98, 2.72)**	**<0.001**	**0.35 (0.28, 0.42)**	**0.11**	**<0.001**
Pain Catastrophizing Scale (possible range 0 – 52)	**1.65 (1.44, 1.89)**	**<0.001**	**0.47 (0.41, 0.52)**	**0.25**	**<0.001**
Anxiety-HADS (possible range 0 – 14)	**1.30 (1.16, 1.46)**	**<0.001**	**0.26 (0.19, 0.32)**	**0.07**	**<0.001**
Depression-HADS (possible range 0 – 14)	**1.47 (1.30, 1.66)**	**<0.001**	**0.29 (0.24, 0.36)**	**0.09**	**<0.001**
Pain Distribution^{+*} n (%)	**1.26 (1.13, 1.40)**	**<0.001**	**0.12 (0.05, 0.18)**	**0.01**	**<0.001**

Table continued on next page

Rows in bold indicate significant associations (p<0.05)

Standardised coefficients for Risk Ratio (RR), beta (β) and R^2 reported.

+Pain Distribution measured on the body pain manikin was coded as present when individual reported knee pain plus other pain below the waist

Table 5-4(Cont.). Prediction of pain persistence and persistent pain severity at year 1 follow up by baseline self-report traits and PPT in unadjusted models.

	Pain persistence at year 1		**Persistent pain severity**		
Traits	RR (95% CI)	p	β (95% CI)	R^2	p
Cognitive Impact* (possible range 0 – 4)	**1.45 (1.29, 1.63)**	**<0.001**	**0.36 (0.30, 0.42)**	**0.13**	**<0.001**
Fatigue*(possible range 0 – 4)	**1.27 (1.13, 1.42)**	**<0.001**	**0.22 (0.16, 0.29)**	**0.05**	**<0.001**
Sleep*(possible range 0 – 4)	**1.90 (1.66, 2.19)**	**<0.001**	**0.56 (0.51, 0.61)**	**0.33**	**<0.001**
Symptom duration*#; years (possible range 0 – 79)	**1.17 (1.03, 1.32)**	**0.013**	0.06 (-0.01, 0.13)	0.002	0.102
PPT and radiographic scores	(n=204)		(n=133)		
Proximal tibia PPT (kPa)	0.79 (0.58, 1.07)	0.125	-0.18 (-0.39, 0.02)	0.02	0.083
Sternum PPT (KPa)	0.82 (0.61, 1.12)	0.214	-0.16 (-0.37, 0.04)	0.02	0.110
Medial Joint Line (KPa)	**0.65 (0.47, 0.89)**	**0.009**	**-0.27 (-0.46, -0.07)**	**0.06**	**0.008**
Lateral Joint Line (KPa)	**0.68 (0.49, 0.93)**	**0.017**	**-0.27 (-0.50, -0.08)**	**0.06**	**0.007**
Radiographic OA severity	**0.68 (0.49, 0.93)**	**0.017**	**-0.27 (-0.50, -0.08)**	**0.01**	**0.007**

Rows in bold indicate significant associations (p<0.05). Standardised coefficients for Risk Ratio (RR), beta (β) and R^2 reported.

Table 5-5. Prediction of pain persistence and persistent pain severity at year 1 follow up by baseline self-report traits and PPT in adjusted models.

	Pain persistence at year 1		**Persistent pain severity**		
Traits	RR (95% CI)	P	β (95% CI)	R^2	p
Central Mechanisms	**2.13 (1.37; 3.31)**	**0.001**	**0.47 (0.25; 0.68)**	**0.29**	**<0.001**
Neuropathic-like symptoms	**2.25 (1.39; 3.63)**	**0.001**	0.22 (-0.02; 0.45)	0.17	0.069
Catastrophizing	**1.94 (1.29; 2.91)**	**0.001**	**0.48 (0.32; 0.65)**	**0.37**	**<0.001**
Anxiety	**1.56 (1.08; 2.25)**	**0.018**	**0.38 (0.19; 0.57)**	**0.25**	**<0.001**
Depression	**1.95 (1.23; 3.09)**	**0.004**	**0.23 (0.02; 0.44)**	**0.21**	**0.032**
Cognitive Impact*	**1.62 (1.09; 2.41)**	**0.016**	**0.39 (0.17; 0.62)**	**0.24**	**0.001**
Pain Distribution*†	**1.58 (1.14; 2.19)**	**0.006**	0.01 (-0.19; 0.22)	0.14	0.912
Fatigue*	1.42 (1.00; 2.00)	0.050	0.12 (-0.10; 0.35)	0.14	0.283
Sleep*	**1.98 (1.29; 3.05)**	**0.002**	**0.62 (0.45; 0.79)**	**0.45**	**<0.001**

Table continued on next page

Models adjusted for demographic variables (age, sex and BMI), radiographic OA severity and symptom duration.

Rows in bold indicate significant associations (p<0.05). Standardised coefficients for Risk Ratio (RR), beta (β) and R^2 reported.

* Measured by single items.

†Pain Distribution measured on the body pain manikin was coded as present when individual reported knee pain plus other pain below the waist.

Table 5-5(Cont.). Prediction of pain persistence and persistent pain severity at year 1 follow up by baseline self-report traits and PPT in adjusted models.

	Pain persistence at year 1		**Pain persistence at year 1**		
PPT Scores	RR (95% CI)	P	β (95% CI)	R^2	p
Proximal tibia PPT (kPa)	0.97 (0.66; 1.41)	0.868	-0.07 (-0.29; 0.15)	0.13	0.528
Sternum PPT (KPa)	0.97 (0.66; 1.44)	0.896	-0.08 (-0.29; 0.13)	0.13	0.458
Medial Joint Line (KPa)	0.77 (0.50; 1.18)	0.227	-0.32 (-0.55; -0.09)	0.20	0.006
Lateral Joint Line (KPa)	0.78 (0.53; 1.17)	0.230	-0.23 (-0.46; 0.002)	0.16	0.053

Models adjusted for demographic variables (age, sex and BMI), radiographic OA severity and symptom duration.
Rows in bold indicate significant associations (p<0.05).
Standardised coefficients for Risk Ratio (RR), beta (β) and R^2 reported.

The relationship between baseline Central Mechanisms trait and persistent knee pain severity remained significant in models adjusted for age, sex, BMI, radiographic OA severity, and symptom duration (β=0.46; p<0.001, Table 5-5). After adjustment for demographic variables, radiographic OA severity and symptom duration, persistent pain severity was also significantly predicted by self-report traits of catastrophizing, anxiety, depression, and cognitive impact (range β=0.23 to 0.63, p<0.035), and by medial joint line PPTs (β=-0.29, p=0.013)(Table 5-5). All self-report and clinical traits explained a significant proportion of pain severity (R^2 range = 0.13 to 0.37, p<0.05) in adjusted models.

5.6.4. Prognostic characteristics of the Central Mechanisms trait

ROC curves demonstrated good performance of baseline scores for the Central Mechanisms trait in distinguishing pain persistence cases from resolved pain cases in an unadjusted logistic regression model (AUC=0.70; 95%C.I.=0.60,0.77; n=1471). The performance of the Central Mechanisms trait model was further improved when it was adjusted for age, sex, BMI, symptoms duration, and radiographic OA severity (AUC=0.78; 95%C.I.=0.71,0.85; n=204, p=0.007)(Figure 5-1).

The performance of other predictors, including age, sex, BMI, PPTs and radiographic OA severity, in distinguishing pain persistence cases from resolved pain cases, was each improved significantly (p<0.05) when the Central Mechanisms trait was included in each logistic regression model (AUC range=0.69 to 0.74, Table 5-6).

Overall study findings were consistent when CFA scores for the Central Mechanisms trait were employed (Appendix 12.2,*p371* to Appendix 12.4., *p374*).

5.7. Results Summary

In this cohort of 1471 individuals with knee pain at baseline, 66% reported knee pain persistence at 1-year follow-up. This study demonstrated that knee pain persistence at 1-year follow-up is predicted by the self-report Central Mechanisms trait, consisting of 8 component traits (anxiety, depression, catastrophizing, neuropathic-like pain, fatigue, sleep disturbance, pain distribution, and cognitive impact) that can be easily assessed in clinical

practice or epidemiological research. These associations were independent of age, sex, BMI, radiographic OA severity, and symptom duration.

Table 5-6. Central Mechanisms trait score improves performance of clinical predictors for pain persistence at 1 year-follow up.

	AUC (95% CI)		
Predictors	Predictor only	Predictor + Central Mechanisms trait score	P value
Central Mechanisms trait	**0.70 (0.60, 0.77)**	**-**	**-**
Age	**0.53 (0.44, 0.62)**	**0.71 (0.63, 0.79)**	**0.001**
Sex	**0.51 (0.44, 0.59)**	**0.70 (0.61; 0.77)**	**0.001**
BMI	**0.64 (0.56, 0.72)**	**0.72 (0.64, 0.80)**	**0.038**
Symptom duration	0.62 (0.54, 0.71)	0.70 (0.62, 0.78)	0.108
Radiographic OA severity	**0.62 (0.57, 0.68)**	**0.73 (0.65, 0.80)**	**0.001**
Proximal Tibia PPT	**0.55 (0.44, 0.66)**	**0.70 (0.59, 0.79)**	**0.025**
Sternum PPT	**0.51 (0.40, 0.62)**	**0.62 (0.58, 0.79)**	**0.014**
Medial Joint Line PPT	**0.58 (0.48, 0.69)**	**0.70 (0.59, 0.79)**	**0.046**
Lateral Joint Line PPT	**0.54 (0.43, 0.65)**	**0.69 (0.59, 0.79)**	**0.022**

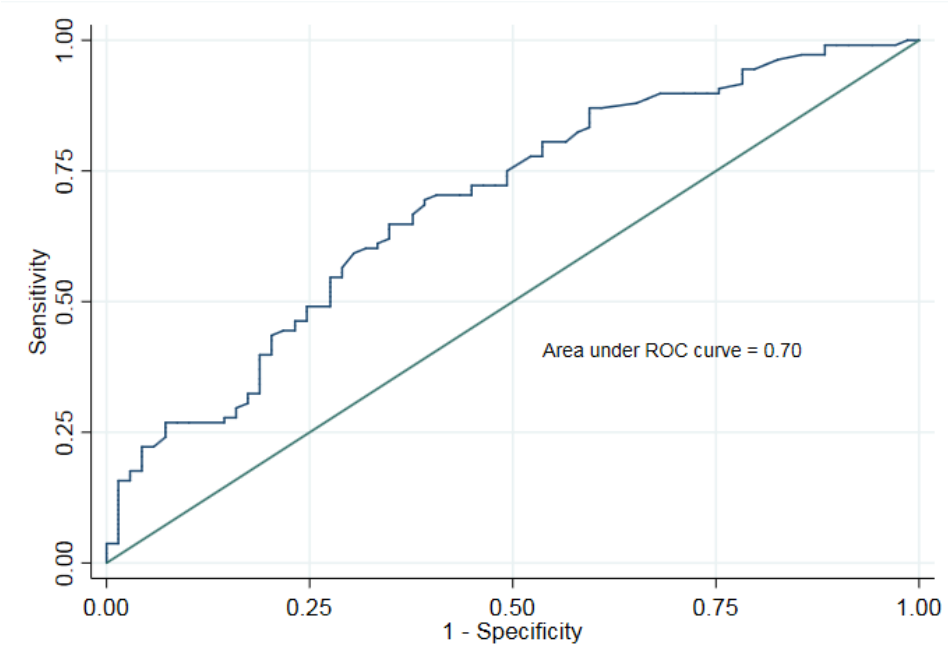
Rows in bold indicate significant model improvement (p<0.05)
AUC – Area Under the Curve Analyses performed across individuals who underwent radiographic and QST assessment at baseline (n=204)

This study shows that a composite trait, combining items representative of 8 component traits which each contributes to central pain mechanisms, predicts cases in whom pain will persist or resolve with an AUC of 0.70, indicating acceptable discrimination.(Mandrekar, 2011) Prediction of pain outcomes by the Central Mechanisms trait depended on each of its 8 component traits, underlining the complexity of central pain processing.

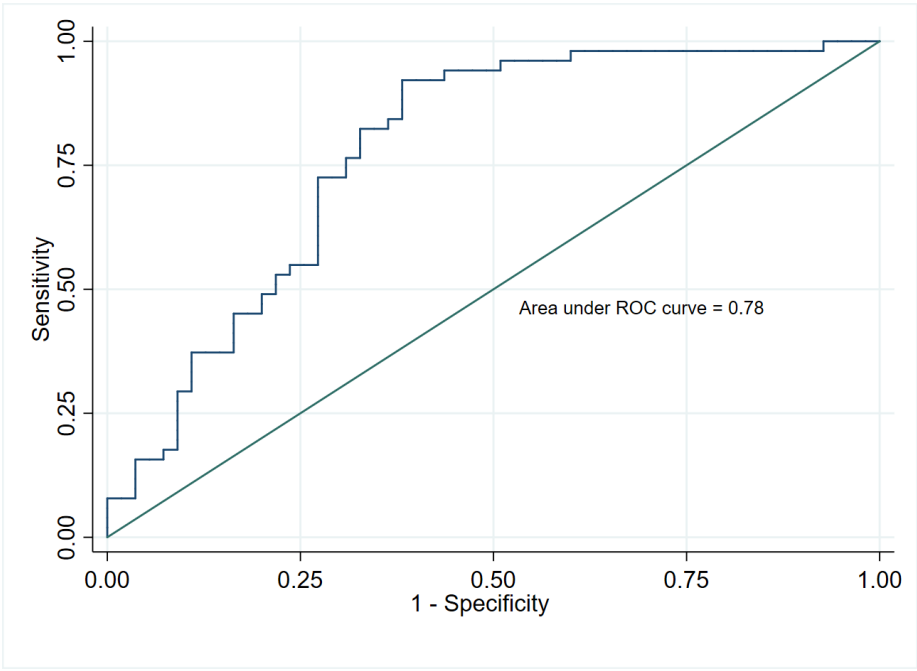
The self-report Central Mechanisms trait showed better discriminatory properties than other predictors of OA knee pain, including tibiofemoral radiographic OA severity present within the (AUC = 0.56), and PPT

(AUC=0.59). Thus, a simple questionnaire comprising 8 items could help identify individuals with poor prognosis for knee pain persistence.

Figure 5-1. Receiver Operating Characteristic (ROC) curve for prediction of pain persistence by Central Mechanisms trait scores in unadjusted and adjusted models.



Crude ROC curve



Adjusted ROC curve
(Model adjusted for age, sex, BMI, radiographic OA severity and symptom duration)

6. THE CENTRAL ASPECTS OF PAIN IN THE KNEE (CAP-KNEE) QUESTIONNAIRE: STANDARDIZATION AND DEVELOPMENT.

6.1. Outline

This chapter presents findings from the development of the CAP-Knee questionnaire, derived from the eight items (*initially included within the KPIC baseline survey*), shown to associate with a QST measure of central pain mechanisms. The original version of the CAP-Knee items were revised based on interpretations provided by individuals with knee pain. The final version of the CAP-Knee will be assessed in further thesis chapters (Chapter 7).

6.2. Introduction

In addition to nociceptive pain arising from within the knee joint, central mechanisms also contribute to the knee OA pain experience (Mease, Hanna, Frakes, & Altman, 2011). Optimal management of knee OA pain requires that characteristics specific to these mechanisms are identified and targeted during treatment to allow an effective response (Mease et al., 2011). As discussed in earlier (0), Imaging and QST markers might indicate the presence of centrally augmented pain, but these approaches are resource-intensive during normal clinical encounters, and are still experimental. A concise composite self-report tool is therefore needed to help classify underlying knee pain mechanisms within the heterogeneous knee pain population.

In light of this, the CAP-Knee questionnaire which comprises of items measuring specific psychological and somatic traits linked to QST markers of central mechanisms, was developed for mechanism-based classification of individuals with knee OA pain. Each trait measured by items within the CAP-Knee have been demonstrated to have significant relationships with QST markers of central pain mechanisms, and with pain outcomes irrespective of radiographic disease severity (Chapters 4 and 5).

A good item in a questionnaire is one that is relevant to both the researchers' agenda and each potential respondent's experience and knowledge. Cognitive interviewing is increasingly used as a step in the refinement of survey questions and Patient Reported Outcome Measures (Knafl et al., 2007). Cognitive interviewing techniques allows questionnaire developers to

determine whether the questionnaire measures what they intend, and that respondents understand and correctly interpret items - thus showing content validity of the item (Patrick et al., 2011). Evaluation of question responses using cognitive interviews therefore identifies and documents what questions measure, how individuals interpret these questions, and identifies differences (*e.g. patterns of interpretation*) in responses. Tourangeau (1984) developed a simple yet elegant model of the survey response process, and highlights four major cognitive processes (*including comprehension, recall, decision, or response processes*) that respondents are generally presumed to engage in when attempting to answer survey questions. Cognitive interviewing is likely to be an effective means for identifying potential problems related to any of the four cognitive processes before the problems are encountered repeatedly in the fielded survey (Efremova, Panyusheva, Schmidt, & Zercher, 2017).

This study hypothesizes that each CAP-Knee item works well across individuals with knee pain, and that researcher interpretation of the CAP-Knee items aligns with that of the individuals reporting knee pain with or without OA..

6.3. Aims and Objectives

6.3.1. Aims

The aims of this study are to understand participants' interpretation of items included within the CAP-Knee questionnaire.

6.3.2. Objectives

1. To identify recurring themes for each item, and to categorize whether or not emerging themes are aligned with the intended meaning.
2. To identify the CAP-Knee items that are difficult to understand, and to determine the causes of these problems based on Tourangeau's response model.
3. Revise problematic CAP-Knee items based on identified causes of problems and themes.

6.4. Methods

6.4.1. Outline

For important clinical decisions to be made using the scores from the questionnaire developed as part of this project, it was important to standardise the format of shortlisted items selected for inclusion within the questionnaire – The CAP-Knee questionnaire. The CAP-Knee study was designed primarily to obtain interview and questionnaire data from a proportion of the local adult population aged 40 and over, who were naïve to the questions included within the newly developing questionnaire - the CAP-Knee questionnaire.

The main aim of this study was to employ qualitative approaches in order to understand the individual's interpretation of the questions included within the CAP-Knee. Where interpretations provided by participants differed from the researchers' interpretation, the items were revised and retested. Items found to work well were included within the final version of the CAP-Knee.

Thus, this study sought to ensure that the standardised CAP-Knee items, which originally originated from the KPIC baseline survey (Chapter 2.2), showed content validity as measures of traits included within the CAP-Knee.

6.4.2. Study design

The CAP-Knee study is a cross sectional multi-centre study of community dwelling adults within Nottinghamshire. Participants' discussions for the CAP-Knee items were qualitatively assessed in this study.

6.4.3. Ethics

The CAP-Knee study protocol was approved by the Nottingham Research Ethics Committee 2 (NREC Ref: 17/EM/0480).

6.4.4. Participants and Recruitment

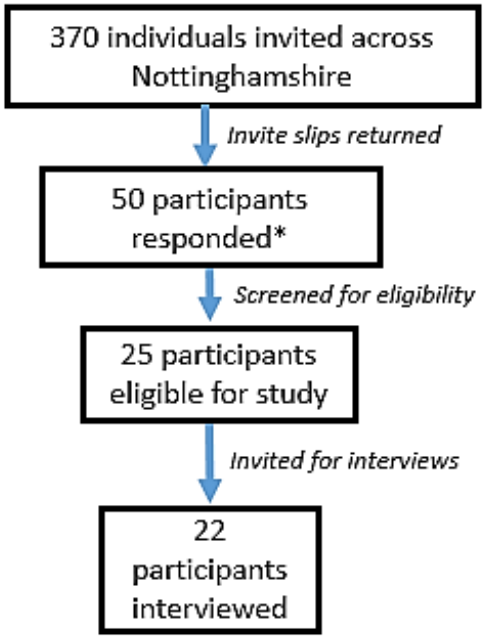
Study participants around Nottinghamshire were recruited from 4 General Practices, and from individuals expressing research interest with ongoing studies conducted within Academic Rheumatology department at the University of Nottingham.

Men and women aged 40 years old or over with current knee pain on most days of the past month, who were able to provide written informed consent,

and able to read and speak English were eligible for inclusion in the study. Exclusion criteria for participants were: any acute or chronic condition that impacts on capacity to consent and understand the information; and any known inflammatory musculoskeletal condition such as Rheumatoid Arthritis.

GPs within Nottingham were approached via the Clinical Research Network (East Midlands). The proportion of individuals recruited at baseline are illustrated in Figure 6-1.

Figure 6-1. Recruitment flowchart for the 'CAP-Knee' study.



*39 out of 50 individuals responding to study consented to further contact and were therefore screened for study eligibility.

Individuals identified by each GP received an invitation letter to the study from their GP introducing the study aims and objectives. Participants also received a participant information sheet, a reply slip for participants to indicate whether or not they would like to be contacted about the study, as well as an enclosed pre-paid envelope addressed to Academic Rheumatology (University of Nottingham) at Nottingham City Hospital.

Participants expressing interest in the study provided their personal details, including full name, address and post code, phone numbers and/or email addresses within the reply slips for further contact. Participants expressing interest in the study were contacted to ensure eligibility and to schedule interview dates and times.

All Participant facing documents, including the invitation letter, reply slip, participant information sheet, consent form and study survey are provided within Appendix 4, *p303* to *p316*.

6.4.5. CAP-Knee study baseline survey

The survey (Appendix 4.1., *p303*) collected self-report information pertaining to participants' demographic details (age, gender, date of birth, weight and height), lifestyle factors (smoking status, and alcohol intake) and physician diagnosed conditions following completion of the interview. Weight and height data were measured to calculate body mass index (BMI), which was classified according to the World Health Organization criteria (World Health, 1995).

Other information on medications and medical history, the standardized CAP-Knee, and other questions on joint aches and pains, and addressing activities and general health were also included in this survey.

6.4.5.1. The CAP-Knee questionnaire

The items included within the CAP-Knee originated from previously validated questionnaires included within the KPIC baseline survey (Chapter 2.2.5). Items within the KPIC baseline survey which were selected for inclusion within the CAP-Knee originated from previously existing questionnaires and were formatted differently across different dimensions.

Questionnaire refinement I:

Particularly, the original version of the selected items varied based on the Likert response options (ranging from 4 to 6 point scales across items), question formatting (statement versus questions), and recall time for each item (ranging from past month to past week).

The CAP-Knee, a composite measure of central mechanisms was constructed by including eight items about anxiety, depression, catastrophizing, cognitive impact, sleep, fatigue, pain distribution and neuropathic-like pain. The original format for CAP-Knee items varied across different dimensions, and were there therefore rewritten and standardised for inclusion within the CAP-Knee based on the criteria below:

Likert response options:

Items included within the CAP-Knee originated from previously validated questionnaires and varied based on the Likert response options (ranging from 4 to 6 point scales across items). All items were assigned four-point response options, with response categories coded as ‘0’ = not at all; ‘1’ = sometimes; ‘2’ = often, and ‘3’ = always. An even number of response options was selected over an odd number of response options in order to avoid unwanted equivocation (Kulas & Stachowski, 2009). An even number of response options forces respondents to make at least a weak commitment in the direction of one of the extremes and to avoid neutral responses from respondents (Kulas & Stachowski, 2009). Hence, the four point approach forces respondents to one extreme or towards the other.

Response anchors: frequency vs. Intensity

Some items were measured originally using intensity terms, while the other items were measured using frequency terms. Rating the frequencies of physical and psychological symptoms is important in screening for the presence or absence of the underlying trait being investigated by the scale (Kline, 2005). In many cases, items which represent a measure of emotion are often defined as the sum of frequent events of the measured domain. Frequency terms have also been reported to show greater stability across time, compared to intensity terms (Krabbe & Forkmann, 2012). Response anchors for items 1 to 7 were therefore rated based on frequency, rather than intensity.

Experience recall – item time frames

Recall periods differed for the items in their original formats, with some assessing the occurrence of traits within “the past month” or “the past week”. Previous evidence suggests that a 1-week recall period is adequately reliable for evaluation of other relevant pain-domains, such as sleep and depression, in individuals reporting chronic pain conditions (Sadosky, Dukes, & Evans, 2009). Thus items 1 to 7 were based on a 1-week recall period.

Item 8, the body pain manikin measuring pain distribution, enquires about pain for most days in the last 4 weeks, intended to represent musculoskeletal pain persisting beyond the acute phase.

Question format and tenses

Questions using the Likert scale typically present a statement (Malhotra, 2006). Thus, items initially presented in a question rather than statement format, were rewritten as declarative statements. Double barrelled (*a question that touches upon more than one issue, but allows only for one answer*) statements were avoided. All items were rephrased from present to past tenses in order to match the past experiences of the domains experienced by the respondents.

In conclusion, addressing all of the above dimensions allowed item rewriting from the original to the newly standardized format. Response categories of 'never', 'sometimes', 'often' and 'always' are employed for the first seven items. The categories are ordered in terms of implied frequency and for the first 6 items, the higher the frequency, the higher the degree of problems measured by the item. In order to disrupt non-substantive responding, the depression item (item 7) was reverse worded (Weijters & Baumgartner, 2012), so that the higher the frequency, the lesser the degree of depressive symptom reported. The final item measuring pain distribution was measured using a body pain manikin, with knee pain and other pain reported below the waist, classified as the presence of centrally augmented pain in individuals (Chapter 4.6.3).

Each of these dimensions were addressed to allow item and questionnaire revision within a standardized questionnaire format. Items were phrased as statements, and response options provided using a unified format.

Questionnaire refinement II

A refined version of the standardized CAP-Knee were evaluated by 7 individuals with arthritic pain who formed the Patient and Public involvement (PPI) groups at the Nottingham University Hospitals NHS Trust. The questionnaire was initially completed by the PPI volunteers, who were then asked to identify any problems with content, language or layout of the CAP-

Knee. This exercise allowed further improvement of the items, questionnaire layout, and instructions, before administration to the CAP-Knee study participants.

6.4.6. Cognitive Interviews

Cognitive interviewing is a psychologically oriented method for empirically studying the way in which individuals mentally process and respond to survey questionnaires (Willis & Artino, 2013). Cognitive interviews are investigative in nature and provide insight into potential sources of errors, patterns of interpretation, and factors that could affect the response process. Cognitive interviews were conducted in the Academic Rheumatology department at the University of Nottingham. Participants were asked to complete the CAP-Knee before the interview commenced. During the interview, verbal probing techniques were based on probes prepared a priori and included within the interview guide (Appendix 5, *p317*). Probes were developed for each of the four-stage question response model as described by Tourangeau 1984: (i) comprehension of the question; (ii) retrieval of relevant information needed to answer it; (iii) a range of judgment or estimation processes that are used to integrate and edit this information; and finally, (iv) a response process in which the individuals convert their internally constructed representation of the answer, to one that constitutes their answer to the question, either in spoken or written form (*e.g., saying "yes" rather than providing an uncertain, conversational response*) (Tourangeau, 1984). This response model allows the questionnaire developer to elicit problems or comments regarding the completion (Beatty & Willis, 2007; Willis, 2005).

The interviews were audio-recorded. Anonymised audio recordings were transcribed verbatim using a transcription service (Clayton Research Support), to generate the data.

6.4.7. Clinical assessment procedures

To determine the proportion of participants with clinical presence of OA according to the ACR classification (Altman et al., 1986), each knee was examined (Doherty & Doherty, 1992). To fulfil the ACR criteria for knee OA (Altman et al., 1986), participants had to present with at least 3 of any of the 6 features: (i) knee pain, (ii) aged 50 years or over, (iii) crepitus on active motion, (iv) knee joint tenderness, (v) no palpable warmth over the knee, (vi)

minimal stiffness (less than 30 minutes). The data collection form for each clinical assessment criterion is provided within Appendix 6 (*p323*).

6.4.8. Data management

Each participant was allocated a unique study identifier number at baseline, which was linked to audio recordings and physical assessment data. All data were entered directly into a pre-prepared form within Microsoft Access 2007 database. The data were entered in text or number format where relevant, and limited to the participant response for each variable, in order to minimise erroneous scoring. Any missing observations coded as 999. The anonymised audio recording data, transcripts, physical assessment and survey data were appropriately catalogued and stored within the Department of Academic Rheumatology, University Of Nottingham.

6.5. Qualitative Analysis

The interviews were audio-recorded and anonymised audio recordings were transcribed verbatim using a transcription service, to generate the data. The transcripts were then checked for accuracy by checking against recording, and any personal identifiers were removed. Thematic- and content- analysis of the transcripts informed decisions on item revision based on apriori criteria defined by the researchers. Throughout the analysis, disagreements or questions were discussed and interpretations were validated with the research team. For each item, potential themes were identified, defined and refined by attributing definitions and names. Team validation minimised the influence of researcher subjectivity and preconceptions on identifying potential themes (Lewis, 2015).

6.5.1. Quality indicators for qualitative data

To assess saturation of codes and themes (*when no new information is forthcoming from interviews),* transcripts were ordered chronologically and then grouped in quartiles of 5 and 6 transcripts (Turner-Bowker et al., 2018). Newly established concept codes or themes for each subsequent transcript group were compared with those derived from the preceding group. The absence of new concept codes or themes in the last transcript group was interpreted as evidence that saturation was achieved.

As described in Chapter 2.3.3.1, Inter-rater reliability (IRR) was accomplished by coding of a subset of transcripts (n=7) by two researchers (KAA and RJ), and comparing each pair of coded transcripts for differences. A random subset of the interview transcripts (n=6) were coded by an independent researcher (RJ) in order to assess reliability of coding between both coders - *IRR* (Campbell, Quincy, Osserman, & Pedersen, 2013). For both coders, during coding, each detail of the transcript was compared to the coding scheme (Appendix 7, *p324*). Agreements and disagreements between coders were tallied for each participant by directly comparing the codes applied to the same (or similar) excerpts. Cohen's weighted kappa (K_W) was used to determine the level of IRR (Cohen, 1960), with kappa values of 0.75 or greater signifying excellent agreement (Landis & Koch, 1977). Differences in interpreting the codes were discussed until consensus was reached. Based on the discussions, the description of each code was made more precise or new specific definitions added to ensure use of the codes were consistent (Kennedy, 2017).

6.5.2. Item Revision

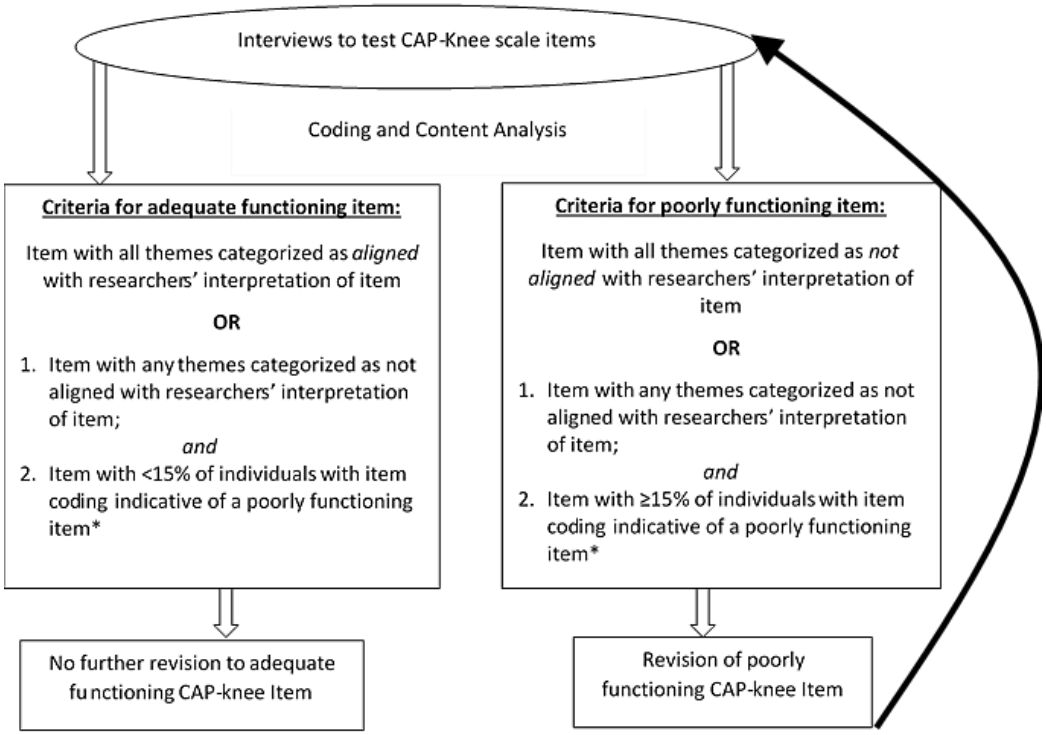
Themes identified for each item were categorized as either being "aligned" or "not aligned" to the intended interpretation of the item. Items were revised if all the themes emerging from discussions about the item were categorized as not aligned to the intended interpretation of the item.

Where a mixture of aligned and not aligned themes were identified from discussions, items were revised if ≥15% of participants provided responses indicative of poor item performance (*including complete non-alignment, complete retrieval difficulty, uncertain initial response and no response consistency*) ((Cannell, Oksenberg, Kalton, Bischoping, & Fowler, 1989; Desimone & Le Floch, 2004; Fowler Jr, 1992) - (Figure 6-2).

No consensus on cut-off points for identification of problematic items is provided in the literature on cognitive interviews. Cut-off points of 50% (Efremova et al., 2017), 20% (Zukerberg, Moore, & Von Thurn, 1995), and 30% (Nicklin et al., 2014) have been applied previously in the literature to identify poorly functioning items. However, in this study, a more conservative cut-off of 15% (Blair, Ackermann, Piccinino, & Levenstein, 2007; Chernyak, Ernsting, & Icks, 2012; Fowler Jr & Fowler, 1995) was applied.

All analyses were conducted in NVivo 12 qualitative software programme (International, 2018).

Figure 6-2. Analysis stages and item revision criteria for the CAP-Knee items.



*Codes indicative of poorly functioning items: complete non-alignment of comprehension, complete retrieval difficulty, uncertain initial response, or inconsistent response formulation.

6.5.3. Thematic analysis

Thematic analysis involves the search for, and identification of, common themes that extend across an entire interview or set of interviews (DeSantis & Ugarriza, 2000). Themes were extracted in this project based on the definition that themes are "an abstract entity that brings meaning and identity to a recurrent experience and its variant manifestations" (DeSantis & Ugarriza, 2000).

Themes identified in this project attempted to explore the range of interpretations specific to each item within the CAP-Knee based on participant experiences. As such, both latent- (*underlying meaning of content such as the interpretation of an interview*) and manifest- (*evidence that is directly seen*) aspects of the data were considered (Braun & Clarke, 2006). In order to guide

item revision, themes were subsequently categorized based on whether or not they were aligned to the researcher's interpretation of each item.

An open coding approach was employed during thematic analysis (Strauss & Corbin, 1998), whereby codes applied during this process were derived from the text (*inductive approach*), and not a priori (Hsieh & Shannon, 2005). Inductive codes were assigned to segments of data that described a theme observed in the text (Boyatzis, 1998). Text was analysed line-by-line in order to compare interpretations provided by participants, thus allowing coding of the data in every way possible (Böhm, 2004). Unlike coding for conceptually similar events (Corbin & Strauss, 1990), the line-by-line coding forces the researcher to verify and saturate themes, minimizes missing an important category, and ensures relevance by generating codes that fit to the substantive area under study (Holton, 2007).

For each identified theme, quotations by participants are provided. In order to ensure anonymity, the numbers assigned to participants follow each quotation provided.

6.5.4. Content analysis

To provide direction for item revision, content analysis sought to develop informative data to identify problems experienced by participants within any stages of the question response model: comprehension, retrieval, judgement and response formulation (Tourangeau, 1984).

Content analysis is a catch all term covering a variety of techniques for making inferences from text data (Berelson, 1952), is an established means for secondary textual analysis, and involves coding and counting in some form (Hsieh & Shannon, 2005). A summative approach to content analysis was employed, which entails quantifying the proportion of participants with quotes contributing to sub-codes across each item (Hsieh & Shannon, 2005). Content analytic procedures have previously been described to provide a measure of confidence that certain frequencies and distributions accurately portray a data set. However, not all researchers agree that "counting" strengthens the analysis (Elo et al., 2014).

Unlike the open coding approach utilized during thematic analysis, a template coding approach was employed, which involves use of an a priori developed

coding template (Table 6-1), and embraces the researcher's position within the study (Blair, 2015) This deductive process (*where data are tested based on a pre-existing theory*), allowed identification of problems, or the absence of problems, in any of the response model stages proposed to govern how individuals respond to questions (Tourangeau, 1984).

Primary patterns of data based on the cognitive interview guide (Appendix 5, *p317*) were identified, coded, and categorized. Problems were identified based on sub-codes developed for each of the main codes of comprehension (completely-, partially or not completely aligned), retrieval (no-, partial- and complete-retrieval difficulty), judgement (certain initial or uncertain initial judgement) and response formulation (consistent or inconsistent).

To demonstrate rigour in this content analysis process, the extent to which another coder independently classifies material in the same way as the peer researcher, intercoder reliability, was assessed (Burla et al., 2008; Elo et al., 2014). The process of assessing intercoder reliability is analogous to interrater reliability procedures described in Chapter 2.3.3. To assess intercoder reliability in this study, a different researcher, Richard James (RJ), independently coded a subset transcripts. General descriptions of the main- and sub- codes employed by coders in this study are provided within Table 6-1.

Further details of how these codes were applied for each question are provided within the coding scheme (Appendix 7, *p324*). The full text of each transcript was coded and analysed with the aid of the qualitative analysis software programme NVivo 12 qualitative software programme (International, 2018).

Table 6-1. Coding template for content analysis of CAP-Knee.

Main Codes **(Descriptions)**	**Sub-codes** **(Descriptions)**	**Instances for when code should be applied**
Comprehension Respondent interprets the question.	Complete alignment Ability to attend to questions and instructions, and to identify the focus of the question	Use for references made to interviewer's questions: • "What does this question mean to you?" • "Can you paraphrase the question?" • "How would you ask that question?"
	Completely not aligned Overly complex and long, unknown terms, ambiguous concepts	
	Partially aligned Discussion of concepts which pertain to complete alignment of the item's comprehension, and discussion of ambiguous or unknown concepts unrelated to the focus of the question	

Each item in the CAP-Knee was assessed for each of the 4 main codes.
Only one sub-code derived from each of the main codes can be provided for each participant.

Table 6-1(Cont.). Coding template for content analysis of CAP-Knee.

Main Codes **(Descriptions)**	**Sub-codes** **(Descriptions)**	**Instances for when code should be applied**
Retrieval Respondent searches memory for relevant information	No retrieval difficulty Ability to retrieve specific or generic memories related to the question provided.	Use for references to previous experiences that pertain to the specific question.
	Complete retrieval difficulty Misfit between the terms used in the question and the events being described by the respondent (descriptions of memories which do not align with the focus of the question)	Certain references lending to comprehension codes could also lend to retrieval codes
	Partial retrieval difficulty Memories provided both related and unrelated to the question provided.	

Each item in the CAP-Knee was assessed for each of the 4 main codes
Only one sub-code derived from each of the main codes can be provided for each participant.

Table 6-1(Cont.). Coding template for content analysis of CAP-Knee.

Main Codes **(Descriptions)**	**Sub-codes** **(Descriptions)**	**Instances for when code should be applied**
Judgement Respondent evaluates and/or estimates response	Certain initial response Ability to integrate the products of retrieval into a single overall judgement while initially completing questionnaire.	Use for references made to the interviewer's question: "How sure are you of that answer?"
	Uncertain initial response In ability to draw conclusions from features of the retrieval process and/or uncertain of the initial response provided during questionnaire completion	

Each item in the CAP-Knee was assessed for each of the 4 main codes.
Only one sub-code derived from each of the main codes can be provided for each participant.

Table 6-1(Cont.). Coding template for content analysis of CAP-Knee.

Main Codes **(Descriptions)**	**Sub-codes** **(Descriptions)**	**Instances for when code should be applied**
Response selection Consistency and acceptability of provided responses	Consistent response Response format matches requested questionnaire format	Use by assessing the participant's response to each item • Item 1-7: One tick per item • Item 8: Shaded or marked areas in manikin diagram
	Inconsistent response	
	Incomplete response options/format	

Each item in the CAP-Knee was assessed for each of the 4 main codes.
Only one sub-code derived from each of the main codes can be provided for each participant.

6.6. Results

6.6.1. Participants Characteristics

A total of 22 interviews were completed between February 2018 and May 2018, mean duration 29 min (range: 16 min to 57 min). The median age of participants was 66 years (IQR = 59 to 74 years), the median BMI was 30kg/m2 (IQR = 26.6 to 34.7 kg/m2), and 15 out of the 22 participants (68%) were women (Table 6-2).

All participants reported knee pain and 20 participants (91%) self-reported an arthritic diagnosis (general arthritis or OA) from their doctor. Following examination of both knees across participants, 21 (95%) fulfilled the ACR clinical classification criteria for knee OA at any joint, of which 10 (48%) had unilateral OA, and 11/21 (50%) had bilateral OA.

Evaluation of the cognitive interview data indicated that saturation was achieved at the end of the fourth transcript group (group 1, n=6; group 2, n=5; group 3, n=6; group 4, n=5). For 7 transcripts chosen at random, individual coders (KAA and RJ) had an inter-observer reliability (weighted kappa, Kw) of 0.78.

6.6.1. Content analysis findings

Sixteen of the 22 (73%) individuals interviewed for this study provided at least one response that met the criteria for a poorly functioning item across the CAP-knee questionnaire (*Completely not aligned comprehension, Complete Retrieval Difficulty, Uncertain Initial Response*) – Table 6-3.

For each item, details of the proportion of individuals coded according to each category, and sub-category are provided within Appendix 13 (*p375* to *p394*). Less than 50% of individuals provided responses that were indicative of poor item function items measuring traits of anxiety (0%), depression (9%), catastrophizing (5%), cognitive impact (32%), sleep (5%), fatigue (23%), and pain distribution (0%) - Table 6-3. However, more than 50% of participants provided responses that were indicative of poor item function for the neuropathic-like pain item (59%).

For the neuropathic pain item, one individual (interview 4) showed responses related to all three codes which are indicative of poor item function.

Table 6-2. Characteristics of the sample.

Participant	Age (years)	Gender (Male/Female)	BMI (kg/m^2)
1	77	Female	34.7
2	58	Female	63.0
3	60	Female	30.2
4	82	Female	29.0
5	68	Female	32.6
6	62	Female	24.5
7	59	Female	36.0
8	43	Male	30.9
9	71	Male	31.7
10	50	Female	42.2
11	81	Female	24.1
12	74	Female	35.7
13	75	Female	22.5
14	67	Male	44.4
15	59	Female	26.6
16	83	Male	28.1
17	66	Male	27.4
18	70	Female	28.3
19	55	Female	19.2
20	63	Male	30.1
21	63	Male	26.5
22	71	Female	-

The first 17 interviews were conducted based on the original version of the CAP-Knee questionnaire. The last 5 interviews were conducted using the revised version of the CAP-Knee questionnaire.
- = One participants did not provide self-report data on weight and height, thus BMI could not be estimated.

Table 6-3. Number of participants with responses related to codes of poor item function across each item.

Items (Interviews = 22)	Completely not aligned comprehension	Complete Retrieval Difficulty	Uncertain Initial Response	Total
Neuropathic-like pain ('Cold or heat touching my knee was painful')*	7 (41%)	4 (23%)	6 (35%)	10 (59%)
Fatigue ("I generally felt tired")	3 (14%)	0 (0%)	3 (14%)	5 (23%)
Cognitive impact ("Knee pain stopped me concentrating on what I was doing")	7 (32%)	5 (23%)	1 (5%)	7 (32%)
Catastrophizing ("I kept thinking about how much my knee hurts")	0 (0%)	0 (0%)	1 (5%)	1 (5%)
Anxiety ("In general, I got sudden feelings of panic")	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Sleep ("Knee pain affected my sleep")	0 (0%)	1 (5%)	1 (5%)	2 (9%)

Table continued on next page
*17 interviews conducted for this item
**5 interviews conducted for this item

Table 6-3(Cont.). Number of participants with responses related to codes of poor item function across each item.

Items (Interviews = 22)	Completely not aligned comprehension	Complete Retrieval Difficulty	Uncertain Initial Response	Total
Depression (“I generally still enjoyed the things I used to enjoy”)	0 (0%)	0 (0%)	2 (9%)	2 (9%)
Pain Distribution (“The final question is about ‘pain that 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. And by pain, we mean aching and discomfort, but we don’t mean pain due to feverish illnesses such as flu.”)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Item 1 revised: Neuropathic-like pain (‘Cold or heat e.g. bath water, on my knee was painful’)**	0 (0%)	0 (0%)	1 (20%)	1 (20%)

*17 interviews conducted for this item
**5 interviews conducted for this item

However, for other items included within the CAP-Knee, none of the study participants provided responses related to all three codes indicative of poor item function (Appendix 13.10, *p396*).

For each individual, codes related to poor item function were only observed for a maximum of 2 items (Table 6-4).

Table 6-4. Summary table showing proportion of participants with responses related to codes of poor item function.

	Problem present within…		
	1 item	2 items	≥3 items
Completely not aligned comprehension	6 (27%)	5 (23%)	0 (0%)
Complete Retrieval Difficulty	7 (18%)	1 (4%)	0 (0%)
Uncertain Initial Response	13 (59%)	1 (4%)	0 (0%)

6.6.1. Thematic analysis findings

Fifteen themes were identified (Table 6-5), which are described here and illustrated by participant quotes.

Neuropathic-like pain: "Cold or heat on my knee was painful"

A key theme of thermal allodynia (theme 1) was expressed by twelve individuals, with discussions focused around the experience of painful sensations due to application of thermal physical stimuli on the knee.

"Well if I put something too cold on it, it really seizes the knee." – Interview 1

Ten individuals discussed painful sensations in their knee due to the cold weather, contributing to another key themes of weather induced pain (theme 2).

"So you know when it's been winter and the cold from the winter makes my leg ache worse!" – Interview 10.

Discussions from six individuals were based on thermotherapy (theme 3). Individuals discussed relief of knee pain following application of hot or cold sensations to the painful knee.

"…because I think hot water sometimes will ease it [knee pain] but it doesn't at times." – Interview 19

The two latter themes of weather induced pain and thermotherapy for the neuropathic-like pain item were deemed to be completely not aligned to the intended meaning of the item. All other key themes (thirteen themes) identified across the eight items were aligned to the intended meaning for each item (Table 6-5).

Fatigue item: "I generally felt tired"

Analysis of the fatigue item identified that seventeen participants interpreted this item with regards to the source of their fatigue (theme 4).

Thirteen participants attributed their fatigue to activities performed during the day, with references made towards how overexertion or participating in physically demanding activities could lead to fatigue (subtheme: physical exertion).

"…in the past week yes, I have because I've been, I had a lot of making stimulation doing work and it's made me feel tired." - Interview 3

Five participants attributed their fatigue to sleep disturbance due to their knee pain (subtheme: sleep disturbance).

"Sometimes the pain of it just keeps me awake, that's why it makes me tired." – Interview 20

Seven participants attributed their fatigue to a variety of other factors, including older age, other comorbidities, (including thyroid problems, diabetes, and fibromyalgia), and medication (subtheme: other fatigue sources).

"But I'm 82. I've also got a thyroid problem. And that can make me tired. So it's a combination thing, I'm afraid." – Interview 4

Table 6-5. List of themes and subthemes identified for each item included within the CAP-Knee.

Item	Key theme (number of individuals contributing to theme out of 22)	Subtheme (number of individuals contributing to theme)
Neuropathic-like pain: "Cold or heat touching my knee was painful"*	Thermal allodynia (n=12)	
	Weather induced pain (n=9)	**N/A**
	Thermotherapy (n=5)	
Fatigue: "I generally felt tired"	Source of fatigue (n=17)	Physical exertion (n=13)
		Sleep disturbance (n=5)
		Other fatigue sources (n=7)
	Fatigue relief (n=8)	N/A
Cognitive impact: "Knee pain stopped me concentrating on what I was doing"	Task distraction (n=10)	N/A
	Hypervigilance (n=12)	

Table continued on next page

*All themes identified from discussions across all participants (n=22), except for the neuropathic-like pain item where the original item was tested in the first 3 rounds of interviews (n=17), and the revised item tested in the last round of interviews (n=5).

Rows in bold indicate themes not aligned with intended meaning of the item.

Table 6-5(Cont.). List of themes and subthemes identified for each item included within the CAP-Knee.

Item	Key theme (number of individuals contributing to theme out of 22)	Subtheme (number of individuals contributing to theme)
Catastrophizing: "I kept thinking about how much my knee hurts"	Causes and consequences (n=11)	N/A
	Avoidance behaviours (n=9)	
Anxiety ("In general, I got sudden feelings of panic")	Fear (n=15)	Fear of what happens in the knee (n=7)
		Fear of falling over (n=6)
		Fear for the future (n=3)
Sleep ("Knee pain affected my sleep")	Sleep disturbance (n=21)	Knee pain interrupting sleep (n=16)
		Knee pain causing discomfort (n=8)
		Other painful sites disturbing sleep (n=7)
	Use of sleeping aids (n=8)	N/A

*All themes identified from discussions across all participants (n=22), except for the neuropathic-like pain item where the original item was tested in the first 3 rounds of interviews (n=17), and the revised item tested in the last round of interviews (n=5).
Rows in bold indicate themes not aligned with intended meaning of the item.

Table 6-5(Cont.). List of themes and subthemes identified for each item included within the CAP-Knee.

Depression: "I generally still enjoyed the things I used to enjoy"	**Social function (n=11)**	**N/A**
	Physical limitation (n=14)	
Pain Distribution: "The final question is about 'pain that 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. And by pain, we mean aching and discomfort, but we don't mean pain due to feverish illnesses such as flu."	Painful sites (n=17)	Nature of pain (n=14)
		Impact of pain (n=5)
		Help-seeking experiences (n=9)
Item 1 revised: Neuropathic-like pain ('Cold or heat e.g. bath water, on my knee was painful')*	Thermal allodynia (n=5)	N/A

Table continued on next page

*All themes identified from discussions across all participants (n=22), except for the neuropathic-like pain item where the original item was tested in the first 3 rounds of interviews (n=17), and the revised item tested in the last round of interviews (n=5).

Rows in bold indicate themes not aligned with intended meaning of the item.

Another key theme of fatigue relief (theme 5) was linked to discussions by eight individuals who described using rest intervals in order to alleviate fatigue. Individuals described needing to stop, sit down, or take a nap in order to feel energetic after experiencing fatigue.

“Well sometimes it tires you out. If it’s aching it does make you tired. So, yeah, I just sit down and rest.” – Interview 9

Cognitive Impact item: “Knee pain stopped me concentrating on what I was doing”

Ten individuals spoke about distraction (theme 6) during discussions focused on the cognitive impact item, and expressed having to stop physical- (e.g. cooking) and/or mental- tasks (e.g. reading) due to their knee pain.

“Um, probably say if you're sitting writing or something, would you be able to concentrate if your knee was hurting you? And if you ask me that, I would probably say I would be able to concentrate to begin with and then my knee would niggle away at me. I’d have to stop writing and get up and straighten my legs and then go back to it, yeah.” – Interview 11

Analysis of discussions for the cognitive impact item identified a theme of hypervigilance (theme 7), with twelve individuals referring to continuous thoughts about their knee pain and an innate need to be cautious while carrying activities:

“But if say I wanted to get up and go to the toilet, I have to think about it. You know what I mean? So anything you’re doing, it’s kind of there.” – Interview 2

Catastrophizing item: “I kept thinking about how much my knee hurts”

Two key themes were also identified for the catastrophizing item. Eleven individuals described having thoughts about the ‘causes and consequences’ (theme 8) surrounding their knee pain. Participants expressed having thoughts about the consequences that an action or a task they had performed would have on their knee pain.

“…I sometimes wonder if that [step exercise] damaged my knee! Because I used to go all the time.” – Interview 7

Nine individuals also described ‘avoidance behaviours’ (theme 9) due to knee pain and referenced having to adapt their behaviours due to the pain they experienced.

“Um, well if I'm sitting in, say I'm relaxing, and if I move my leg over it’ll start hurting so I'm thinking about, you know, I've got to keep still, you know…” – Interview 21

Anxiety item: “In general, I got sudden feelings of panic”

One key theme of fear (theme 10) was raised by 15 individuals during discussions about the anxiety item. Seven individuals expressed worry concerning the integrity and function of their knees at present (subtheme: fear of what happens in the knee).

“That the knee’s going to pop out. Let’s say going upstairs, sometimes it feels as though the bones have gone ‘bip’ and I think is it going to pop out” – Interview 1

Six individuals described past experiences where they had been frightened about almost falling expressed a subtheme: fear of falling over.

“I’m so afraid of going, falling, or tripping over something because I can't lift my bloody leg high enough.” – Interview 16

Three individuals discussed worry about the impact that their knee pain could have on their future (subtheme: fear for the future).

“Because I think to myself oh if I can't, what am I going to do, if I can't walk, what will I do.” – Interview 15

Sleep item: “Knee pain affected my sleep”

Three major themes were identified across participant discussions relating to interpretation of the sleep item.

Discussions from twenty-one participants contributed to a key theme of sleep disturbance (theme 11). Sixteen of these participants specifically discussed being woken up by their knee pain, specifically due to moving their knees during sleep (subtheme: knee pain interrupting sleep).

“Yes it means it’s exclusively when I turn over. I’ll be fast asleep, and you know, you turn over onto your position, and that’s when I feel it. Yeah. So it sort of jolts me awake.” - Interview 4

Eight of the nineteen participants also discussed feelings of restless while in bed, and failure to get comfortable due to their knee pain (subtheme: Restlessness). These individuals made references to attempting to get comfortable in bed by adjusting their knees.

“Yeah, the pain just seems to get worse at night when I lie down, like, yeah, just turning from one side from another.”- Interview 20

Discussions by seven individuals contributed to another key theme of other painful sites disturbing sleep (subtheme three: Other painful sites disturbing sleep).

“I wouldn't say it’s [knee pain’s] woke me up quite like that in the past week, there’s been something added to that, that’s been part of waking me up, just generally because the pain’s across all the body.”– Interview 6

Eight participants discussed ‘use of sleeping aids’ (theme 12) by describing use of pharmacological (e.g. painkillers, sleeping pills) or non-pharmacological aid (cushions between knees) in order to get back to sleep.

“You know, I’m afraid I do rely on sleeping pills occasionally if things are bad. You know.” – Interview 4

Depression item: “I generally still enjoyed the things I used to enjoy”

Two key themes were identified during analysis of the discussions about the depression item. Eleven individuals interpreted this item with regards to their social function (theme 13), and in some cases, references were made about a decline in social function.

“-But in life in general, I suppose, [long pause] it’s OK, but I just can’t join in, you know, with the things that he [husband] likes to do, and whatever, and we used to do together. So -”- Interview 2

Fourteen individuals referred to physical limitation (theme 14) hindering their enjoyment of activities.

“Yeah, well I've not really stopped enjoying them. Yeah, OK, I've been limited to stuff that – I've been just limited, the knee’s limited it, but I've still done it.”- Interview 8

Pain Distribution item: “This final 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.”

One major theme of ‘painful sites’ (theme 15) was discussed by seventeen individuals. Fourteen individuals described pain at the sites where pain was reported (subtheme: nature of pain).

“Well, like, just my left leg, knee there, gives me the actual pain and I say that back bit, it just feels like pinching, like a pinching type of pain.” – Interview 5

Nine individuals discussed how they had sought help for the painful sites reported on the body pain manikin (subtheme: Help seeking experiences).

“But going to the doctors and he said ‘I think you might have fibro-’, ‘I want a second opinion’, so I waited and waited and then went back, then they noticed I had this Meniscus Tear, so that could have been doing it because it puts strains on other bits, but I went to see a consultant and he said ‘you’ve got like fourteen points of the fibromyalgia’…” Interview 10

Five individuals also discussed the impact that the reported painful sites had on their physical function (subtheme: impact of pain).

“It was quite restricting at first. I can't get my arm round the back of my head to do my hair and things like that.” – Interview 11

6.6.2. Item revision

Neuropathic-like pain: “Cold or heat (e.g. bath water) on my knee was painful”

Discussio0ns by individuals were centred on weather induced pain and thermotherapy, which were not in keeping with the intended meaning of

thermal allodynia (Table 6-5). In addition, the original version of the neuropathic-like pain item showed the greatest proportion of individuals with responses indicative of poor item function (n= 10/17, 59%), exceeding the 15% cut-off for the additional item revision criteria. This item was therefore rewritten to provide reference to an example of tangible physical stimuli intended by the developers: ‘cold or heat (e.g. bath or shower water) on my knee was painful’. All five individuals interviewed about the rewritten version of the neuropathic-like pain item provided discussions in keeping with the theme of thermal allodynia (Table 6-5).

6.7. Results Summary

Overall, in participants reporting knee pain irrespective of OA classification, discussions for items included within the 8-item CAP-Knee questionnaire were collapsed into 15 key themes (One Anxiety theme = Fear; two Depression themes = Social function, Physical limitation; two Catastrophizing themes = Causes and consequences, Avoidance behaviours; two Cognitive impact themes = Task distraction, and Hypervigilance; two Sleep themes = Sleep disturbance and Use of sleeping aids; two Fatigue themes = Source of fatigue, Fatigue relief; one Pain distribution theme = Painful sites and three Neuropathic-like pain themes = Thermal allodynia, Weather induced pain and Thermotherapy).

A mixture of aligned and not aligned themes were identified from discussions about the Neuropathic-like pain- and depression-items. More than 15% of participants provided responses indicative of poor item performance for the neuropathic-like pain item only, but not the depression item.

Compared to the original version of the neuropathic-like pain, the rewritten version of the neuropathic-like pain item was considered to work well. This revised item, and the original version of items representing anxiety, depression, cognitive impact, sleep disturbance, fatigue, and pain distribution, formed the final version of the CAP-Knee questionnaire (Appendix 13.11, *p397*).

7. THE CAP-KNEE QUESTIONNAIRE: A PSYCHOMETRIC EVALUATION.

7.1. Outline

This chapter discusses the psychometric properties of a newly developed self-report measure of 'Central Mechanisms': The CAP-Knee questionnaire.

Data from 250 participants completing the CAP-Knee questionnaire were assessed to establish the construct validity, internal consistency, and ceiling and floor effects of the questionnaire. Fit between the Rasch model and the data was assessed to further demonstrate the measurement properties of the CAP-Knee. The repeatability of the CAP-Knee was also assessed within a subgroup of participants who completed the questionnaire twice within a 1-month interval (n=76), in order to determine the repeatability of the CAP-Knee over time.

This chapter concludes by providing a summary of the study findings.

7.2. Introduction

Imaging and QST technologies for assessing mechanism based changes in individuals with knee pain are resource intensive during normal clinical encounters. For busy physicians, an ideal test would be short, straightforward, and reliable for outcome assessment, and subgrouping patients. Once an individual reports knee OA pain, a self-report tool is needed that can provide a simple, structured, consistent manner for clinicians and researchers to confirm the presence or absence of central pain mechanisms, and to monitor the change of these central mechanisms over time. It is also important that dimensionality is assessed, in order to ensure that the constructs purported to be measured by tool, are indeed measured by the tool. Reliability (internal consistency) is essential to ensure that the scores obtained from the tool is not due to chance. Modern psychometric techniques such as the Rasch methodology are typically employed to assess dimensionality of the tool. Demonstrating dimensionality ensures that the constructs purported to be measured by tool is indeed measured by the tool. Rasch transformed scores further allows the questionnaire to be applied as an outcome measure which is able to detect change (Tennant & Conaghan, 2007).

Eight self-report items that measure of psychological and somatic traits (including Neuropathic-like pain, Fatigue, Cognitive impact, Catastrophizing, Anxiety, Sleep disturbance, Depression and Pain distribution), measured a unifying, overarching trait termed ‘central mechanisms’, which predicted PPTs at a distal site in individuals with knee pain – a QST index for central pain mechanisms (Chapter 4). Some of these self-report traits have been shown to associate with experimental- markers for central knee OA pain mechanisms (Ali et al., 2017; Brown et al., 2016; Campbell et al., 2015; Harden et al., 2003; Lluch et al., 2017; Lluch et al., 2014; Lluch Girbes et al., 2016; Petersen et al., 2015; Petersen et al., 2016; Woolf, 2011; Wylde et al., 2017), and predict persistent pain following peripherally targeted treatment (Ali et al., 2017; Harden et al., 2003; Petersen et al., 2015; Petersen et al., 2016; Wylde et al., 2017). Previous work also showed good prognostic characteristics for the Central Mechanisms trait in discriminating between persistent and resolved pain cases (Chapter 5).

Each of the eight items measuring the relevant psychological and somatic traits linked to Central Mechanisms (Chapter 4) were included within a composite questionnaire - the CAP-Knee.

However, application of any questionnaire in clinical and research setting will benefit from demonstration of favourable psychometric properties following scale evaluation (Boateng et al., 2018). Psychometrically sound, self-report tools gives us clinically useful information, for use of the tool across a variety of patients and settings when administered by different clinicians and researchers. Traditional psychometric properties such as validity, reliability and responsiveness of the questionnaire needs to be assessed (Boateng et al., 2018; Nunnally & Berntein, 1994). Content validity for the items included within the CAP-Knee was previously demonstrated (Chapter 6).

Thus, this study hypothesizes that the CAP-Knee questionnaire is a psychometrically valid and reliable questionnaire for use across individuals with knee pain.

7.3. Aims and Objectives

7.3.1. Aims

The overall aim for this study was to evaluate the psychometric properties of a developing questionnaire – the CAP-Knee.

7.3.2. Objectives

The study objectives sought to:

(i) examine the Rasch properties of the CAP-Knee;
(ii) assess the construct validity of the CAP-Knee;
(iii) assess the repeatability of CAP-Knee summary scores; and
(iv) assess the internal consistency of the CAP-Knee.

7.4. Methods

7.4.1. Outline

Data from the Investigating Musculoskeletal Health and Wellbeing (IMH&W) study provided secondary data which was analysed for the purposes of addressing objectives within the current thesis.

The IMH&W study was designed to obtain questionnaire data from an adult population aged 18 and over. This study was developed under the musculoskeletal theme of the National Institute for Health Research (NIHR) Nottingham Biomedical Research Council (BRC) which seeks to understand the trajectories of pain, disability and frailty in individuals with musculoskeletal disease, over time.

Within the scope of this project, the IMH&W study contributed to the identification of eligible participants with data which would contribute towards further psychometric assessment of the final version of the CAP-Knee.

7.4.2. Ethics

The CAP-Knee study protocol was approved by the London Central Research Ethics Committee (REC Ref: 18/LO/0870).

7.4.3. Study design

The IMW&H study is a community-based questionnaire survey comprising a sample of the general population of East Midlands.

7.4.4. Participants and recruitment

IMH&W Study participants in the East Midlands region were recruited from GPs and from individuals expressing research interest in studies conducted within the NIHR Nottingham BRC.

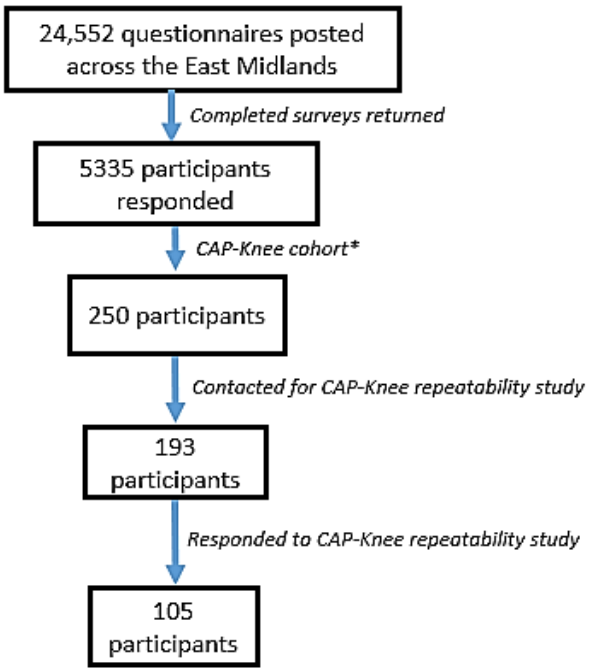
Men and women aged 18 years old or over, from a range of ethnic backgrounds, who have or are at risk of developing musculoskeletal conditions and were able to provide written informed consent, were eligible for inclusion in the study. Exclusion criteria for participants were: persons who might not adequately understand verbal explanations or written information in English, or who have special communication needs.

Regional GPs within Nottinghamshire, Leicestershire, Lincolnshire and Derbyshire were approached via the Clinical Research Network (East Midlands). At baseline, postal questionnaires sent to participants were accompanied by a covering letter from their GP introducing the study aims and objectives, an enclosed pre-paid envelope to Academic Rheumatology (University of Nottingham) at Nottingham City Hospital. At the end of each postal questionnaire, participants were asked to indicate whether or not they would be willing to be contacted about further research. Participants expressing interest in the study provided their personal details, including full name, address and post code, phone numbers and/or email addresses for further contact. Participant details were handled according to the Data Protection Act, 1998. Electronic data including the study database are held securely and are password protected. Source documents are held securely, in a locked cabinet with a locked room. Access to information is limited to study staff and investigators and any relevant regulatory authorities. All the information provided will be kept securely for at least 7 years to enable regulatory authorities to check that the study has been conducted properly.

7.4.4.1. CAP-Knee psychometric assessment cohort

The IMW&H study began baseline recruitment from May 2018, with baseline recruitment scheduled to end by July 2019. As shown in Figure 7-1., a subset of participants responding to the baseline postal questionnaires, and consenting to further contact, were screened for inclusion within the CAP-Knee psychometric assessment study.

Figure 7-1. IMW&H/CAP-Knee psychometric study recruitment flowchart.



*Data from the first 250 participants who completed the CAP-Knee within the IMW&H study and met the inclusion criteria for psychometric assessment of the CAP-Knee were assessed.

Eligibility criteria for the psychometric assessment study differed to that for the IMW&H study. Men and women aged 40 years old or over with current knee pain on most days of the past month, who were able to provide written informed consent, and able to read and speak English were eligible for inclusion in the psychometric assessment study. Exclusion criteria for participants were: any acute or chronic condition that impacts on capacity to consent and understand the information; and any known inflammatory musculoskeletal condition such as Rheumatoid Arthritis.

Based on their response to the initial survey, 250 participants recruited for the IMW&H study were identified as eligible for psychometric assessment of the CAP-Knee. For repeatability assessment of the CAP-Knee, 193 out of the 250 participants, were contacted via mail to complete the CAP-Knee at follow-up. Participants were mailed the final version of the CAP-Knee, a cover letter explaining the aims and objectives of the repeatability study, a participant information sheet, and a pre-paid envelop within a 7-day interval of responding to the CAP-Knee included within the IMW&H study survey. Repeatability was only assessed across individuals whose knee pain remained persistent over both study time points.

7.4.5. Self-report assessment

The IMH&W study collected information on participant demographic characteristics, medications and medical history, joint aches and pains, and included the final version of the CAP-Knee.

The CAP-Knee consists of eight items which assess each of the eight traits linked to Central Mechanisms of knee pain, comprising Neuropathic-like pain, Fatigue, Cognitive impact, Catastrophizing, Anxiety, Sleep disturbance, Depression and Pain distribution. The first seven items were scored on a 4-point Likert scale, ranging from '0' representing 'never', to '3' which represents 'always'. The eighth item which measures pain distribution is a binary item. To allow the pain distribution scores to be in line with scores from the first 7 items, individuals were given a score of '3' for reporting knee pain in the presence of other painful sites below the waist. Absence of other painful sites below the waist was scored as '0'. Thus, the summary scores of the CAP-Knee ranged from 0 to 24.

7.4.6. IMH&W Data management

Each participant was allocated a unique study identifier number at baseline, which was linked to follow-up data. All data were double entered directly into REDCAP cloud, using an online pre-prepared form constructed by the database manager. The data were entered in text or number format where relevant, and limited to the participant response for each variable, in order to minimise erroneous scoring. The extracted tsv data file of the REDCAP forms were then saved within an Microsoft Access database to allow data cleaning and sharing. Any missing observations coded as 999. The paper questionnaires were appropriately catalogued and stored within the Department of Academic Rheumatology.

7.4.6.1. Quality of data entry

To examine the quality of data entry, a sample of 100 questionnaires from the 250 identified for further assessment, were verified against the data entered within the REDCAP database. A direct visual comparison was undertaken between the data recorded in the database and that written in the questionnaires. Each question was examined for errors and these were recorded in a separate Microsoft Excel spreadsheet. For each question, the

total number of mistakes and a percentage error was calculated. An error below 2% was considered acceptable. Only one of the questions scored above a 2% difference (item 8 of the CAP-Knee, 34%) due to a systematic issue related to data entry where the categorization of pain distribution as ‘absent’ or ‘present’ was observed. The data entry instructions were revised to resolve this issue for further data entry, and data cleaning procedures were applied to the database for the IMH&W study population to derive the correct responses for the item.

This procedure was repeated for the time 2 CAP-Knee responses and a high level of data entry quality was observed, with overall error rate of 0.02%.

7.5. Statistical Analysis

Participant characteristics, including age, sex and BMI are described. Means and SDs are presented where data was found to be normally distributed. For non-normally distributed data, median and ranges were presented instead. Spearman’s correlation was used to assess univariate associations between CAP-Knee scores and demographic characteristics, including age, sex and BMI. Paired t-tests were used to assess differences in demographic characteristics between individuals included in the rasch study cohort (n=250), compared to the subgroup of participants included in the repeatability study (n=76) (Armitage et al., 2008).

Reliability and repeatability were assessed using Stata 14.2 (StataCorp, 2015). Item redundancy and internal consistency were investigated by calculating Cronbach's alpha (α), with values < 0.70 indicating poor internal consistency, and values >0.90 indicating item redundancy (Streiner, 2003; Streiner & Kottner, 2014). To investigate repeatability (test–retest reliability) of the questionnaires scores, the ICC for overall scores was calculated (Koo & Li, 2016), as previously described in Chapter 2.3.3.1. Floor and ceiling effects were considered present if >15% of respondents achieved the highest/lowest possible tool scores (Terwee et al., 2007).

Using the SEM framework described in Chapter 2.3.2, CFA of the CAP-Knee (time 1 data, n=250) was evaluated in M*Plus* version 7.4 (Muthén, 2012).

7.5.1. Rasch Analysis

Rasch analysis employed here reflect analytic recommendations described in Chapter 2.3.5 (Tennant, Horton, & Pallant, 2011), using the R software package (version 3.4.1 for Linux; http://cran.r-project.org/package=TAM) (Robitzsch et al., 2019). The appropriate form of the polytomous Rasch model for the CAP-Knee was determined by conducting the likelihood ratio test. Data for which the likelihood ratio test was significant were analysed using the partial credit model. Unlike the rating scale model, the partial credit model does not assume that threshold distance is uniform across all items.

Deletion and rescoring of misfitting items were considered in subsequent models, and iterative testing was employed (Lundgren & Tennant, 2011). Bonferroni corrections for multiple analyses were used when appropriate. The person separation index (PSI) was calculated to estimate measurement reliability of the CAP-Knee, with PSI= >0.70 set as the cut-off for reliability (Wright, 1999). The person-item distribution was plotted to consider how well the persons in the sample match traits being measured by the questionnaire, also known as the targeting of the scale to the sample.

True population scores were employed for further validation analyses. Performance of Rasch transformed- and true population- summary or item scores, were compared in further analyses where possible.

7.6. Results

7.6.1. Participant Characteristics

Histograms for each measure within the entire baseline population (n=250) and for the CAP-Knee at both time points (n=76) are presented within Appendix 14 (*p398*). Baseline characteristics for participants included in baseline assessment of the CAP-Knee (n=250) are summarized in Table 7-1.

Of the 105 participants who responded at both baseline and follow-up, data from 29 participants were excluded from the repeatability analyses because they did not complete all the items in the questionnaires.

Table 7-1. Baseline characteristics for study population.

	Overall baseline population (n=250)	Repeatability subgroup (n=76)	P value
Age (*yrs*)	71 (64 – 77)	71 (66 – 78)	0.63
Sex (*n, %*)	158 (63%)	49 (72%)	0.08
BMI (kg/m^2)	28 (25 – 32)	28 (24 – 32)	0.49
CAP-Knee score (possible scores: 0-24)	8 (6 – 12)	8 (6 – 11)	0.15

Data are median and interquartile range (IQR), except where indicated.

As shown in Table 7-1, participant characteristics for the baseline psychometric analysis group (n=250) did not differ significantly (p>0.05) from participant characteristics for the subgroup of participants included in the repeatability study (n=76). The median interval between the first and second assessments was 20 days (interquartile range = 17 – 24 days). Scores from the CAP-Knee were weakly correlated with lower age (r=-0.14, p=0.02), higher BMI (r=0.25, p=0.003) and being female (r=0.16, p=0.01).

7.6.2. Rasch Modelling

Likelihood ratio test showed significant differences (p<0.001) between the partial credit formulation and the rating scale model. Thus the partial credit version was performed for each analysis.

7.6.2.1. Rasch properties of the 8-item model

Initial fit of the CAP-Knee to the Rasch model revealed a significant chi-square value for the item-trait interaction [X^2(df) = 63(28); p<0.001], suggesting misfit between data and the model (Table 7-2). Overall person fit statistics had a mean of 0.01, suggesting the average scores was very close to what was expected, with an acceptable SD of 1.09, however, the summary item fit statistics indicated misfit between the data and the model (Table 7-2). The cognitive impact item showed misfit (Table 7-3). The sleep disturbance item exhibited disordering of the step difficulty (i.e. the difficulty of a higher step was lower than that of its adjacent lower step) – Appendix 15.1, *p400*.

Figure 7-2 shows the person–item threshold distribution for the 8-item model and indicates that while the scale was well targeted, a disordered response threshold can be observed for the sleep disturbance item. Eleven out of 246 t-tests were significant, which represented 4.43% (Binomial CI: 2.23-7.79%) of the total tests (Table 7-2). Four items (Neuropathic-like pain item, fatigue item, anxiety and depression items) showed misfit for outfit values in one or more response options, suggesting that observed responses for these categories did not concord with the expected model – Appendix 15.1, *p400*.

Principal components analysis of the residuals identified items that positively (neuropathic-like pain, fatigue, anxiety, depression and pain distribution) and negatively (cognitive impact, catastrophizing and sleep disturbance) loaded on the first component. Analysis of the CAP-Knee item residuals demonstrated no correlations ($r<0.3$) between items. None of the items exhibited non-uniform DIF for age or sex. None of the items showed uniform DIF for age, however, the pain distribution item showed uniform DIF ($p=0.03$) for sex.

Scale and item re-appraisal.

Items were re-scored by collapsing response categories until the thresholds demonstrated sequential levels of severity. This resulted in a decrease in the number of response categories from 3 (*'Always'*) to 2 (*'Often'*) for the first seven items. The pain distribution item was scored as '1' when other painful sites below the waist was reported by individuals with knee pain. Thus, the scores for the revised scoring system ranged from 0 to 15.

The 8-item model, following collapsing of response categories performed just as well as the initial 8-item model (Table 7-2 and Table 7-3). The questionnaire was found to be unidimensional, with no local dependency of items observed, however, the pain distribution item still showed uniform DIF for sex. As seen in Table 7-2, fit to the Rasch model was only achieved following removal of the item showing unacceptable misfit (cognitive impact item, Table 7-3) and the item showing DIF for sex (pain distribution item).

A 6-item model, where misfitting pain distribution and cognitive impact items were excluded, performed even better than both 8 item models (Table 7-2 and Table 7-3).

Table 7-2. Summary item-person interaction statistics for the partial credit model.

Model	X2 (df)	P value	Item fit residual (mean)	Item fit residual (SD)	Person fit residual (mean)	Person fit residual (SD)	PSI	Percentage of significant *t*-tests (CI)
8 items - no changes to scale	63 (28)	<0.05	0.79	1.35	0.01	1.09	0.80	4.43% (2.23% to 7.79%)
8 items – 8 items rescored	52 (28)	<0.05	0.19	1.34	0.02	1.28	0.73	4.43% (2.23% to 7.79%)
6 items - 6 items rescored[+]	16 (15)	0.06	0.26	1.35	0.00	1.29	0.70	4.18% (2.02% to 7.56%)
Ideal value	*-*	*>0.05*	*0*	*1*	*0*	*1*	*≥0.70*	*<5%*

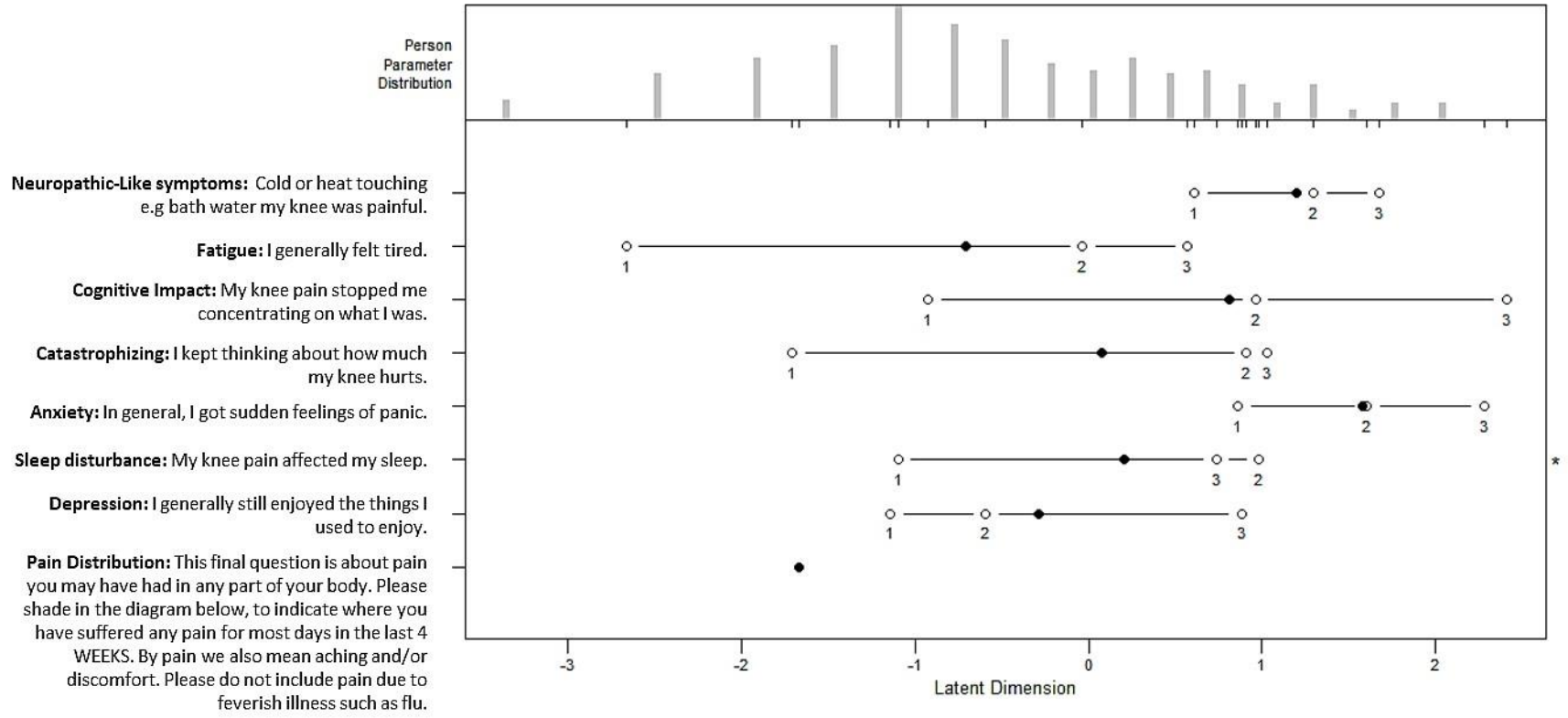
[*] Categories 2 and 3 for NP-like symptoms, fatigue, anxiety, sleep and depression collapsed.
[+] Categories 2 and 3 for all items collapsed.
PSI = Person Separation Index

Table 7-3. Fit statistics for items included in 8- item models.

Items	8 item-model				8 item-model, all items rescored				6 item-model, all items rescored			
	Difficulty logit	SE logit	Outfit MNSQ	Infit MNSQ	Difficulty logit	SE logit	Outfit MNSQ	Infit MNSQ	Difficulty logit	SE logit	Outfit MNSQ	Infit MNSQ
Neuropathic- like pain	2.03	0.11	0.86	0.91	1.60	0.12	0.86	0.92	1.56	0.12	0.81	0.85
Fatigue	-0.12	0.08	0.98	0.99	-0.99	0.11	0.94	0.94	-0.96	0.11	0.88	0.91
Cognitive impact	**1.09**	**0.09**	**0.59**	**0.59**	**0.45**	**0.10**	**0.59**	**0.60**	-	-	-	-
Catastrophizing	0.59	0.08	0.72	0.72	-0.09	0.10	0.73	0.75	-0.08	0.10	0.77	0.80
Anxiety	2.39	0.12	0.85	0.94	1.96	0.13	0.88	0.93	1.92	0.13	0.82	0.92
Sleep disturbance	0.78	0.09	0.70	0.72	0.21	0.10	0.67	0.69	0.21	0.10	0.70	0.71
Depression	0.11	0.08	1.02	1.07	-0.64	0.10	0.93	1.02	-0.62	0.10	0.83	0.93
Pain distribution	0.17	0.15	1.23	1.16	**-0.45**	**0.16**	**1.37**	**1.19**	-	-	-	-

MNSQ = Mean square residual; SE = Standard Error. - : Items excluded from analysis of model.
Negative difficulty logits indicate items that are easier to endorse, and positive measures indicate items that are more difficult to endorse.
Row in bold indicates items with misfitting values for infit or outfit (Normal MNSQ values range between 0.7 and 1.3).

Figure 7-2. Person-Item map for 8-item model.



*Disordered response threshold

Taking into consideration the clinical relevance of each of the 8 items included within the CAP-Knee, the 8-item model with collapsed response categories was deemed as the most appropriate model for use as an outcome measure. Transformed scores for the 8-item model, with all items rescored, are provided in Table 7-4.

Similar to the initial 8-item model, Figure 7-3 and Figure 7-4 illustrates that while the questionnaire was well targeted, a few persons (represented by bars at the top of the histogram) fell outside the range of severity measured by the CAP-Knee items and their categories (represented by the lines below the histogram). Misfit for some response categories were still observed for both the 8-and 6– item model after rescoring (Appendix 15.2, *p403* and Appendix 15.3, *p405*).

7.6.3. Confirmatory Factor Analysis, reliability and repeatability

Factor analysis confirmed the one-factor model for the true population responses (CFI = 0.99; TLI= 0.98; X^2(df)= 37(20); RMSEA= 0.06), and for the Rasch converted responses (CFI = 0.98; TLI= 0.97; X^2(df)= 38(20); RMSEA= 0.08). All eight items loading significantly on to the single latent factor, termed ‘central mechanisms’ (Table 7-5).

Cronbach’s alpha was 0.75 for true population scores and 0.74 for Rasch transformed scores.

The true population summary score for the first seven items were significantly associated with each other (*rho* range = 0.24 to 0.66, p<0.05), except the pain distribution which was only significantly associated with sleep disturbance (*rho* = 0.14; p= 0.02) and fatigue (*rho* = 0.16; p= 0.01). No items were found to be redundant - Appendix 15.4, *p407*. These findings were similar for the Rasch item scores, following collapse of response categories – Appendix 15.5, *p408*.

The repeatability intra-class correlation coefficient ($ICC_{2,1}$) for the true population summary scores and the Rasch transformed scores were exactly similar at 0.91 (95% CI 0.86 – 0.94) and 0.91 (95% CI 0.86 – 0.94), respectively. Of the respondents, 0.4% had the minimum questionnaire scores of 0 and 0.4 % had the maximum scores of 24.

Table 7-4. Score conversion for final 8 item model.

Population score	Rasch Score	True score
1	-6.00	0.00
2	-5.47	0.10
3	-4.95	0.17
4	-4.43	0.28
5	-3.91	0.46
6	-3.39	0.73
7	-2.87	1.12
8	-2.35	1.68
9	-1.83	2.46
10	-1.30	3.48
11	-0.78	4.71
12	-0.26	6.09
13	0.26	7.54
14	0.78	9.01
15	1.30	10.43
16	1.83	11.75
17	2.34	12.81
18	2.87	13.58
19	3.39	14.11
20	3.91	14.45
21	4.34	14.68
22	4.96	14.81
23	5.48	14.89
24	6.00	15.00

Figure 7-3. Person-Item map for 8-item model, with all items rescored.

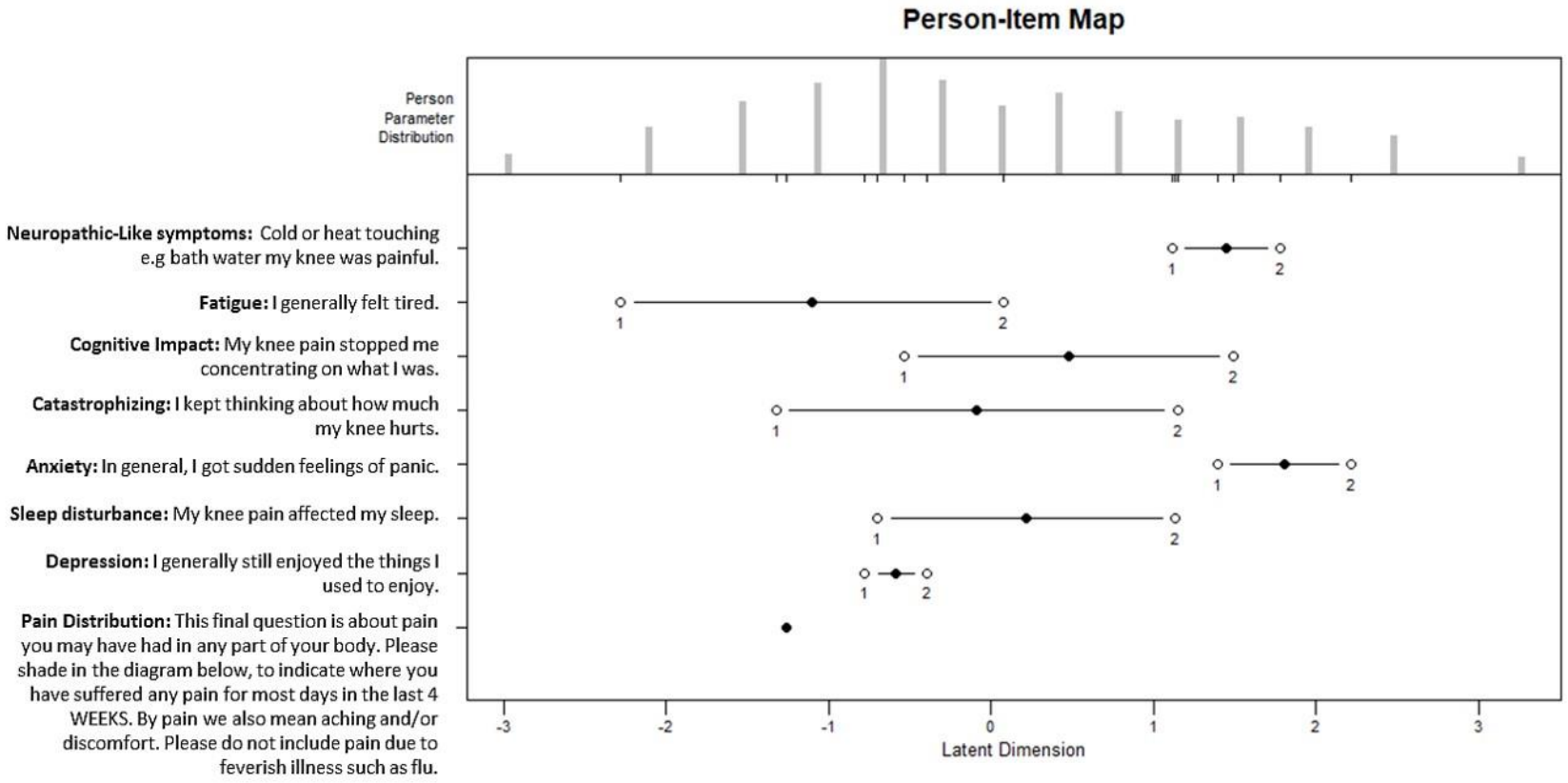


Figure 7-4. Person-Item map for 6-item model, with all items rescored.

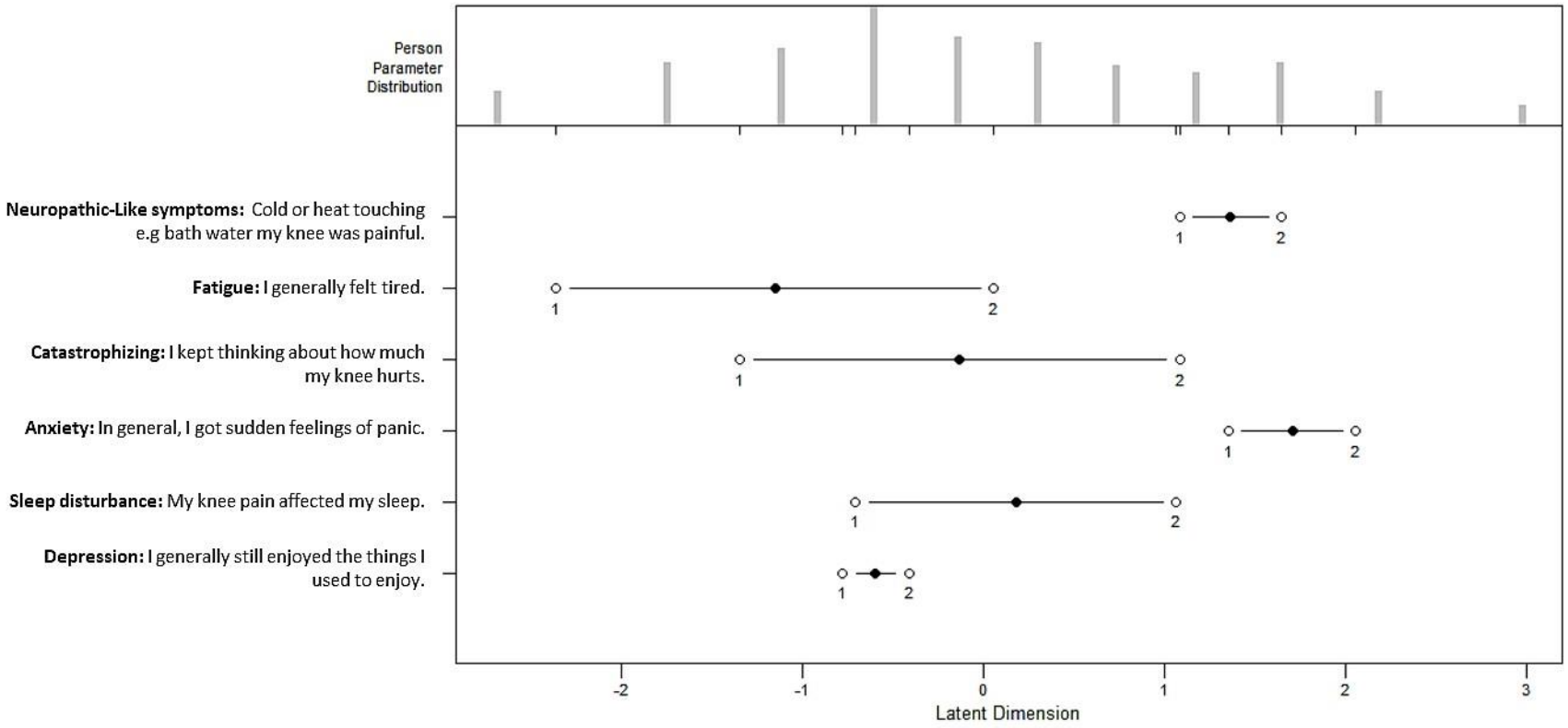


Table 7-5. Item loading for CAP-Knee one-factor model.

Item	Item loading	
	True population item scores	Rasch converted item scores[#]
Neuropathic-Like symptoms: Cold or heat touching e.g. bath water my knee was painful	0.588**	0.559**
Fatigue: I generally felt tired.	0.420**	0.470**
Cognitive Impact: My knee pain stopped me concentrating on what I was.	0.918**	0.864**
Catastrophizing: I kept thinking about how much my knee hurts.	0.830**	0.748**
Anxiety: In general, I got sudden feelings of panic.	0.596**	0.692**
Sleep disturbance: My knee pain affected my sleep.	0.755**	0.736**
Depression: I generally still enjoyed the things I used to enjoy.	0.444**	0.450**
Pain Distribution: This final 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.	0.212*	0.158*

*p<0.05; **p<0.001
[#]Item categories rescored based on final Rasch model

7.7. Results Summary

The CAP-Knee questionnaire was assessed to establish its psychometric properties within a knee pain population. Rasch and CFA approaches confirmed unidimensionality of the CAP-Knee, supporting work in Chapter 4 and 5, which suggests that items representing 8 different psychological and somatic traits all significantly contribute to one latent trait. Following scale

calibration, identification of a good-fitting Rasch model for the data allowed the development of a Rasch scoring conversion table for easy transformation of CAP-Knee scores to interval level scores. These interval level scores will therefore support accurate longitudinal monitoring that could inform future clinical care and research.

The raw and rasch transformed scores for the CAP-Knee showed excellent test-retest repeatability. These findings together support the use of the 8-item CAP-Knee questionnaire within individuals reporting knee OA pain.

8. DISCUSSION

8.1. Overview

This project was driven by the hypotheses that a concise and valid set of self-report items representative of traits which associate with underlying mechanisms of knee OA pain can constitute a newly developed mechanism-based classification tool.

This chapter discusses the main findings of the thesis, summarizes implications of the findings in relation to clinical assessment of underlying mechanisms related to knee pain, and outlines future research directions to allow implementation of the newly developed scale – the Central Aspects of Pain in the Knee (CAP-Knee) scale within research and clinical practice.

8.2. Key findings, interpretations and Caveats

8.2.1. Item generation: Self-report traits associated with peripheral and central pain mechanisms.

Expert and multivariate ESEM statistical approaches were applied in the current study to successfully generate items for the developing mechanisms-based questionnaire. 56 items which measured traits of emotional wellbeing, catastrophic thinking, pain patterns, neuropathic-like pain, sleep/fatigue, pain distribution and cognitive impact, originally included within the KPIC baseline survey (items = 115) were assessed in this study.

In keeping with the thesis objective which sought to identify items that measure traits linked to knee OA pain mechanisms, the dynamic ESEM approach was employed over other existing item selection approaches (e.g. ability of the item to discriminate cases vs. non-cases of measured traits) (Hill et al., 2008). ESEM analysis greatly aided the judgement of whether, and which, items from a factor was most closely related to the relevant traits. Discriminatory properties of shortlisted items in predicting QST measures of central pain mechanisms, and future pain outcomes, are assessed in future chapters (Chapters 4 and 5). Experts in this study only selected items that were relevant to central-, but not peripheral- mechanisms of knee OA pain. The lack of items shortlisted to reflect peripheral mechanisms is consistent with the literature, as no self-report items exists as markers of structural

damage linked to knee OA pain. Thus, the rest of this thesis focuses on the development of a questionnaire which measures underlying central pain mechanisms in a knee OA population.

In the current chapter, ESEM was conducted to reduce the item pool by identifying the two items that showed the strongest contribution, also known as factor loading, to a latent trait measured by a group of items. A total of 11 latent traits (including anxiety, depression, psychomotor agitation, pain intensity, evoked and spontaneous neuropathic-like symptoms, fatigue, helplessness and rumination, constant and intermittent pain) were identified. The 22 strongest loading items to the 11 identified latent traits, as well as the 2 items representing traits of pain distribution and cognitive impact, were further shortlisted for further assessment.

Moderate positive correlations existed across latent traits identified within each of the item groups. Within the emotional wellbeing group of items (items=16), the data supported the superior fit of the three-factor model (*anxiety, depression and psychomotor agitation*). This is in keeping with previous work which identified a three-factor model for the HADS subscale in various chronic conditions (Barth & Martin, 2005; Caci et al., 2003; Friedmann, Samuelian, Lancrenon, Even, & Chiarelly, 2001). Patients with psychomotor agitation frequently present with symptoms of restlessness which is highly associated with depressive symptoms (Perugi, Akiskal, & Micheli, 2001; Sacchetti et al., 2018).

Contrary to reports within the literature of a three-factor structure for the PCS across healthy and pain populations (Sullivan et al., 1995; Van Damme, Crombez, Bijttebier, Goubert, & Van Houdenhove, 2002; Yap et al., 2007), the current study supports a two-factor model (helplessness and rumination) as the best fitting model within a knee pain population. This is consistent with other exploratory analysis in pain outpatient samples where a two- factor structure of helplessness and rumination are reported (Osman et al., 2000).

The full ICOAP questionnaire showed factorial complexity following factorial analysis of the 11-item questionnaire, supporting previous psychometric analysis of the ICOAP which suggests that individual scores from the constant and intermittent subscales be applied over use of the entire questionnaire

scores (Moreton et al., 2012). This recommendation is corroborated by the current study which has identified good model fit in both subscales of the ICOAP when analysed separately, compared to analysis of the full questionnaire. ESEM of each item group for constant and intermittent pain support a one-factor model. Whilst there was improvement following assessment of two factor models within each of the item groups, the item loading patterns did not show biological/theoretical relevance. In addition, there was substantial cross loading across the identified factors, and less than 3 items loading primarily to one factor. Thus, the 2-factor model was rejected, and the one-factor model was selected as the best fitting factor for both item groups.

Consistent with previous reports of a two-factor model (Gudala, Ghai, & Bansal, 2017), the 12- item PainDETECT questionnaire showed good fit for the two-factor model (pain intensity and neuropathic symptoms). However, there was a significant improvement of model fit in the three-factor model (pain intensity, evoked and spontaneous neuropathic symptoms). Findings here are similar to a previous study (Moreton et al., 2015), where the item addressing course of pain did not load significantly onto any of the identified latent factors in the neuropathic like-symptoms item group (loading <0.3).

Good fit for the one-factor model was identified across four of the six items initially selected to represent sleep/fatigue was identified to measure a latent trait of fatigue. Two items representative of fatigue were included within further assessment. Items representing sleep were however included within the shortlisted items from the pain patterns group.

Single items measuring respective traits of cognitive impact and pain distribution were assessed for item redundancy. Prior research has argued that items within a questionnaire items with correlations higher than 0.70 might be redundant (Ferketich, 1991; Taber, 2018). Findings here suggest that these single-item measures of pain distribution and cognitive impact items measure somewhat distinct traits, and were therefore retained within the item pool for further item selection analysis. While no studies exist that have previously assessed the nature of the relationship between traits of pain distribution and cognitive impact in individuals with knee pain, one group demonstrated that cognitive impairments are usually present in individuals presenting with

fibromyalgia, a central sensitization syndrome (Rodriguez-Andreu et al., 2009). This supports the involvement of both traits in central mechanisms.

Items agreed upon by experts as relevant to central pain mechanisms are in keeping with published literature. Many latent traits identified in this study, including rumination, anxiety or depression, have been shown to predict poor response to peripherally acting treatment (Dave et al., 2017; Finan et al., 2013; Forsythe et al., 2008; Hodges et al., 2016; Noiseux et al., 2014; Pinto et al., 2013; Wylde et al., 2018), and other experimental traits linked to central mechanisms (Brown et al., 2016; Bulls et al., 2017; Campbell et al., 2015; Gupta et al., 2007; Harden et al., 2003; Hochman et al., 2013; Kurien et al., 2016; Lluch et al., 2017; Lluch Girbes et al., 2016; Mihailova et al., 2015; Wylde et al., 2015).However, the relationship between markers of central mechanisms and some underlying latent traits identified in this study, including spontaneous and evoked neuropathic-like pain, constant and intermittent pain, and helplessness, are yet to be demonstrated.

Neither of the items representing the latent trait of psychomotor agitation achieved the agreement cut-off during the expert consensus study. While ESEM of the HADS demonstrated correlations between psychomotor agitation and the other latent traits of anxiety or depression, there is a scarcity in the literature implicating the latent trait of psychomotor agitation with chronic pain, or its underlying mechanisms. One group demonstrated associations between psychomotor agitation and severe chronic pain in individuals with major depressive disorder (Rijavec & Novak Grubic, 2012). Further work might benefit from investigating the role that psychomotor agitation might play in the knee pain, as well as with underlying pain mechanisms.

Two items were identified to reflect peripheral mechanisms of OA knee pain following expert consensus measure pain intensity. However, current evidence suggests link between pain intensity and peripheral markers of OA (*including radiographic grades or synovitis*), as well as with QST markers of central pain mechanisms, (*including temporal summation and conditioned pain modulation)* (Lee, Nassikas, & Clauw, 2011). Thus, pain intensity measures cannot be employed for mechanism based classification of individuals. One group suggested that disproportionate, non-mechanical, unpredictable pattern of pain might be central in nature (Lluch et al., 2017). Therefore use of pain

intensity questions as a mechanism based measure requires additional evidence of the underlying structural damage in order to judge whether the reported pain is ‘proportionate’ or ‘disproportionate’. Overall, evidence from this study suggests that items measured within the KPIC baseline survey are insufficient measures of underlying peripheral pain mechanisms.

This study is not without limitation. The traits analysed were limited to those included within the KPIC baseline survey, and initial screening by the researchers may have allowed subjective bias during the initial stage of item selection.

A key objective of the current study sought to provide an item shortlist which are the most representative of the traits which they are purported to measure. Other methodologies seeking to refine item pools have been employed previously in the literature. For example, items are selected based on their ability to screen for relevant outcomes. While there is no consensus in the literature for the methodology to be applied during item development, it is important that the selected approach reflects the research question. Thus, the ESEM methodology provided an efficient approach to addressing this objective. Identifying these representative items allowed determination of content validity for each of the shortlisted item by an expert panel in subsequent work.

All experts involved within the expert rating of the items study originated from a single centre in the UK. The breadth of expertise reflected by experts in this study was representative of multidisciplinary teams (e.g. consultant rheumatologists, orthopaedic surgeons, psychologists and arthritis pain researchers) which are typically involved in the treatment and research of knee pain. It is possible that additional traits not shortlisted in this chapter might further contribute to the identification of pain mechanisms in people with knee pain.

8.2.2. Item selection: Self-report traits associated with a QST measure of central pain mechanisms.

Each of the 8 items contributed significantly to an underlying latent trait, termed ‘Central Mechanisms’ trait. Association between PPTs and the ‘central mechanisms’ trait was not explained by originating questionnaire derived scores, radiographic disease- or pain- severity. Together, these findings support use of a composite tool to identify the extent of central pain augmentation in people with knee pain, regardless of radiographic severity. In addition, this study supports use of a composite tool rather than individual assessment of each trait on a case-by-case basis in clinical practice.

Strength of association between each selected item and PPT was reduced following adjustment for originating questionnaire total score, suggesting at least partial mediation by trait measured within the host questionnaire. However, associations between PPT and items addressing neuropathic-like pain in response to cold or heat, or addressing feelings of panic remained statistically significant even after adjustment for the derived PainDETECT and HADS-anxiety scores. These items might have specific associations with central mechanisms over and above representing neuropathic-like pain or anxiety respectively.

The body pain manikin item was identified as a measure of pain distribution and was selected for inclusion within the developing questionnaire. The current study adds supporting evidence to the presence of other painful sites in individuals with knee pain (Croft et al., 2005; Skou et al., 2013). Previous studies have reported that between 22% and 87% of individuals with knee pain also report other painful sites (Croft et al., 2005; Siemons, ten Klooster, van de Laar, van den Ende, & Hoogeboom, 2013; Skou et al., 2013). This is in keeping with the current study which found that between 10% and 71% of individuals with knee pain met the binary pain classifications employed across manikin pain distribution reports. This suggests that a significant proportion of individuals with knee pain also report other painful sites as seen in the current study. Individuals reporting ‘pain other than knee pain below the waist’ or ‘knee pain plus ≥5/7- or ≥6/23-other painful sites’ on the body pain manikin not only show increased sensitivity at sites distal to the index joint (*indicative of secondary mechanical hyperalgesia due to central sensitization),* but also show hypersensitivity at sites local (*indicative of primary mechanical*

hyperalgesia) and remote to the affected region (*indicative of abnormalities in descending controls*).

One study employing templates illustrating only the lower half of the body showed enlarged pain areas below the waist in patients with symptomatic knee OA, which were associated with other measures of CS (Lluch Girbes et al., 2016). Overall, these results support the notion proposed here to use shading of 'other pain below the waist' on the body pain manikin to classify individuals with centrally augmented knee pain. The current study suggests that the ACR's WSP is a poor discriminator of central sensitization in patients with knee OA, but might be due to the fact that individuals reporting knee pain in the presence of ACR's WSP classification only made up 10% of the knee pain study population.

The small sample size may have influenced the lack of significant findings identified in the current study. Findings from the back pain literature demonstrated that in comparison to individuals with back pain in the presence of Chronic Widespread Pain, individuals with localized back pain showed sensitization specific to a localized site, regardless of disease duration (Gerhardt et al., 2016). Such widespread pain distribution is prevalent in Fibromyalgia, and descending control systems have been implicated as a possible mechanism (Julien, Goffaux, Arsenault, & Marchand, 2005). Together, this suggests that diffuse pain distribution might be present in many localized chronic pain conditions regardless of disease duration, and may involve descending control systems. Loss of descending control systems, may be modifiable in individuals with knee pain following removal of the peripheral drive (Graven-Nielsen et al., 2012), but this was a small study (n=21), and further work is needed to confirm these findings.

Employment of only one modality of QST assessment is a key limitation to this study. PPT has consistently been associated with knee pain in previous studies and displays good measurement properties in people with knee pain (Mutlu & Ozdincler, 2015). Index knee joint-line PPT displayed higher reliability than proximal tibia PPT employed as a measure of CS in this study (Akin-Akinyosoye et al., 2018). Other modalities for assessing central mechanisms, especially those with higher reliability than PPTs, might produce more confident estimates of associations with the trait identified here (Lachin, 2004).

Participant selection within KPIC for PPT assessments was weighted towards an early knee pain sample (pain for < 3 years). Previous studies have demonstrated a lack of association between PPTs and symptom duration in individuals with OA knee pain (Neogi et al., 2015), but further research should determine whether these findings can be generalised to people with longer symptom duration or more severe OA structural change. The current work is also limited due to the cross-sectional approach employed, and longitudinal studies might help disentangle the nature of the relationship between pain severity, peripheral pathology, PPTs, and traits identified in the current study.

Further research should determine whether the central trait identified in the current study might also predict these other indices of central pain mechanisms. Further research should also define clinical thresholds that might predict or represent important response to treatment.

8.2.3. Predictive validity: baseline self-report 'central mechanisms' traits as a predictor of persistent knee pain

In this cohort of 1471 individuals with knee pain at baseline, 66% reported knee pain persistence at 1-year follow-up. This study demonstrated that knee pain persistence at 1-year follow-up is predicted by the self-report Central Mechanisms trait, consisting of 8 component traits (anxiety, depression, catastrophizing, neuropathic-like pain, fatigue, sleep disturbance, pain distribution, and cognitive impact) that can be easily assessed in clinical practice or epidemiological research. Individuals with higher scores on the Central Mechanisms trait (>7) showed a 2-fold higher risk for reporting pain persistence and reported more severe persistent pain at 1 year follow up. These associations were independent of age, sex, BMI, radiographic OA severity, and symptom duration. This study shows that a composite trait, combining items representative of 8 component traits which each contributes to central pain mechanisms, predicts cases in whom pain will persist or resolve with an AUC of 0.70, indicating acceptable discrimination.(Mandrekar, 2011) Prediction of pain outcomes by the Central Mechanisms trait depended on each of its 8 component traits, underlining the complexity of central pain processing. The self-report Central Mechanisms trait showed better discriminatory properties than other predictors of OA knee pain, including tibiofemoral radiographic OA severity present within the (AUC = 0.56), and PPT (AUC=0.59). Thus, a simple questionnaire comprising 8 items could help

identify individuals with poor prognosis for knee pain persistence.In this cohort of 1471 individuals with knee pain at baseline, 66% reported knee pain persistence at 1-year follow-up. Knee pain persistence and persistent knee pain severity were predicted by the self-report Central Mechanisms trait, derived from 8 component characteristics (anxiety, depression, catastrophizing, neuropathic-like pain, fatigue, sleep disturbance, pain distribution, and cognitive impact). The prognostic performance of the Central Mechanisms trait was superior to that of other demographic and clinical factors, including measures of any of the 8 component characteristics or radiographic evidence of OA pathology.

Findings in Chapter 4, following a cross-sectional analysis of KPIC participants with knee pain, demonstrated that the 8 self-report items used in the current study, together defined a single latent trait, and were significantly associated with QST evidence of central sensitisation (reduced PPT at anatomical sites away from the affected joint). Previous interventional studies have also found that pain outcomes can be predicted by self-report measures of psychological distress (Helminen et al., 2016; Lewis et al., 2015), and experimental QST indices of central pain mechanisms (Petersen et al., 2015; Petersen et al., 2016). These findings indicate that pain outcome prediction by these characteristics might be explained, at least in part, by a shared Central Mechanisms trait. Additional characteristics of cognitive impact, catastrophizing, sleep disturbance, fatigue, neuropathic-like pain quality and pain distribution each might contribute to this predictive trait.

A composite score from self-report items, each addressing one of these 8 characteristics, better predicted pain outcomes than did measures of any single characteristic alone. The composite measure of the Central Mechanisms trait in the current study predicted cases in whom pain persisted or resolved with an AUC of 0.70. This indicates acceptable discrimination (Mandrekar, 2010), but also suggests that other factors might contribute to pain outcomes. The Central Mechanisms trait better predicted pain outcomes than did radiographic OA severity. These findings extend previous evidence that central mechanisms might influence pain intensity over and above effects of radiographic joint damage (Finan et al., 2013) or disease duration (Neogi et al., 2015).

Radiographic OA severity within the tibiofemoral compartment (AUC=0.62) significantly predicted knee pain persistence, and combining radiographic OA severity with Central Mechanism scores improved this prediction. Incremental validity was evident when other predictive variables such as radiographic OA were included within the model. These findings suggests that the Central Mechanisms trait might better discriminate future knee pain when other relevant factors are accounted for. The existing literature have proposed that other biological- and social- factors might also predict future pain outcomes (Jinks, Jordan, Blagojevic, & Croft, 2008 {Peters, 2005 #1206) }. Together, factors contributing to the biopsychosocial model of pain may better account for future pain outcomes, and might therefore show better AUC performance than observed in this study. Combining mechanistically discrete factors might further improve pain outcome prediction, as previously found by combining demographic and psychological characteristics (Jacobs et al., 2018).

The current study showed that of the sites investigated by PPT in the current study, only joint line PPT significantly predicted knee pain persistence or severity. Furthermore, PPT predicted pain persistence less strongly (medial joint line PPT AUC=0.59) than did the Central Mechanisms trait, and prediction of pain persistence by PPT was not statistically significant after adjustment for demographic variables, radiographic OA severity and symptom duration. Baseline joint line PPTs might also not predict post-arthroplasty pain (Martinez et al., 2007), although another study found that PPT both at sites local to, and remote from the affected knee predicted pain severity (Wright et al., 2015). Joint line PPTs may be influenced both by peripheral and by central sensitisation, whereas PPT at sites away from the affected joint is more likely to reflect central than peripheral sensitisation (Suokas et al., 2012). That peripheral sensitisation may contribute to poor pain prognosis is also suggested by pain prediction by radiographic OA severity, and by ultrasound evidence of synovitis (Sarmanova et al., 2017). Future studies should explore whether treatments to reduce peripheral sensitisation (e.g. by inhibiting inflammation or blocking nerve growth factor) can reduce knee pain persistence, as well as relieving current pain (Schnitzer et al., 2015).

Prediction of pain outcomes by the Central Mechanisms trait in the current study remained significant after adjustment for PPT scores, suggesting that central mechanisms additional to those indicated by PPT contribute to pain

outcomes. Such mechanisms might include dysregulated descending pain modulation (Suzuki et al., 2004).

This study has several limitations. Only one QST modality (PPT) was employed in the current study, and dynamic modalities such as temporal summation (Neogi et al., 2015), might have greater potential to predict knee pain outcomes. PPT may be influenced by factors other than CS, such as participant reporting styles, attention, participant-researcher interactions, and also peripheral sensitisation. Further work is needed to confirm the nature of the relationship between more reliable estimates of sensitization and the Central Mechanisms trait discussed in this study. However, we show that self-report items have potential to identify in clinical practice, people whose pain is augmented by central mechanisms, where special skills or equipment required for reliable estimation of sensitization might not be available.

These findings help achieve the aim of the KPIC project to identify knee pain traits and risk factors for knee pain progression (Fernandes et al., 2017). However, only a subpopulation of the KPIC cohort underwent radiographic and PPT assessment. Participant selection at baseline (as described in Chapter 2.2.6) was weighted towards an early knee pain sample (younger and shorter symptom duration), although other measured characteristics did not differ significantly from the overall study population. All models adjusted for age and symptom duration, but it remains possible that pain prognosis would be predicted differently in later stages of knee pain and OA.

This measure of Central Mechanisms trait requires validation in an external study population, and across different clinical, community and cultural settings. Most reports evaluating prediction models focus on the issue of internal validity, leaving the important issue of external validity behind. External validation could address the accuracy of the current study findings (Justice, Covinsky, & Berlin, 1999; Knottnerus, 1992; McGinn et al., 2000).

A cut-off score for the Central Mechanisms trait score was not determined in the current study, due to the derivation of the summary scores from the original KPIC item scores. Identifying a cut-off score for the final questionnaire (following revision and standardisation of the 8 selected items within a

composite scale), will provide beneficial information that adds clinical value to the final version of the questionnaire under development in this project.

Additionally, use of the transformed KPIC scores for the Central Mechanisms trait, provided identical results to those obtained from analysis of weighted factor scores. This finding supports employing the transformed scoring (scores ranging from 0 to 3) described in this study, within the final version of developing questionnaire. According to Nunnally “there is overwhelming evidence that the use of differential weights seldom makes an important difference” (Nunnally, 1978). In addition, weighting of the items could make scoring more complicated and, should not be used unless it can be justified.

Future work will benefit from the assessing the final version of the questionnaire for predictive validity (as assessed in the current study), and for concurrent validity (by demonstrating associations between the newly developed questionnaire, and other self-report or objective measures that assess central mechanisms.

In conclusion, we show that a single overall Central Mechanisms trait represented by items addressing 8 individual phenotypic traits, predicts pain persistence and persistent pain severity in people with knee pain. Future research should determine whether a central mechanisms questionnaire can predict treatment responses in people with knee pain, and in other chronic pain conditions where central mechanisms are at play (Giesecke et al., 2004). Such a questionnaire might help identify those destined to experience a poor pain prognosis in the absence of specific intervention, and might indicate central mechanisms that could benefit from non-pharmacological (e.g. cognitive behavioural therapy) or centrally acting pharmacological treatment.

8.2.4. The Central Aspects of Pain in the Knee (CAP-Knee) questionnaire: Standardization and development.

Overall, in participants reporting knee pain irrespective of OA classification, discussions for items included within the 8-item CAP-Knee questionnaire were collapsed into 15 key themes (One Anxiety theme = Fear; two Depression themes = Social function, Physical limitation; two Catastrophizing themes = Causes and consequences, Avoidance behaviours; two Cognitive impact themes = Task distraction, and Hypervigilance; two Sleep themes = Sleep

disturbance and Use of sleeping aids; two Fatigue themes = Source of fatigue, Fatigue relief; one Pain distribution theme = Painful sites and three Neuropathic-like pain themes = Thermal allodynia, Weather induced pain and Thermotherapy).

A mixture of aligned and not aligned themes were identified from discussions about the Neuropathic-like pain- and depression-items. More than 15% of participants provided responses indicative of poor item performance for the neuropathic-like pain item only, but not the depression item.

Compared to the original version of the neuropathic-like pain, the rewritten version of the neuropathic-like pain item was considered to work well. This revised item, and the original version of items representing anxiety, depression, cognitive impact, sleep disturbance, fatigue, and pain distribution, formed the final version of the CAP-Knee questionnaire (Appendix 13.11, p397). This study sought to understand participants' interpretation of items in the newly developed 8-item CAP-Knee questionnaire - a patient report classification tool designed to reflect the presence of underlying central pain mechanisms in individuals with knee pain. Cognitive interviewing, as employed in this study, is a qualitative procedure, analysis does not rely on strict statistical analysis of numeric data but rather on coding and interpretation of the interview itself (Willis & Artino, 2013). With no consensus on how cognitive interviews are analysed, item revision decisions were based on a rigorous approach which included using intensive coding schemes for content analyses in order to classify problems according to Tourangeau's question response model into general categories (Conrad & Blair, 2004). Categorization of identified themes based on consensus within the research team was also employed to supplement the content analyses findings, in order to identify items in need of revision (Peterson et al., 2017).

Except the neuropathic- like pain item, other items representing traits of anxiety, depression, catastrophizing, cognitive impact, sleep, fatigue, and pain distribution were found to work well across participants were found to meet the criteria for adequate function. Therefore, only the neuropathic-like pain item was considered for revision.

Discussions about the neuropathic-like pain item, originating from the painDETECT (Hochman et al., 2011), mainly revolved around the theme of thermal allodynia. Allodynia refers to pain due to a stimulus that does not normally provoke pain (Loeser & Treede, 2008), and is typically assessed using a QST approach (Freeman et al., 2014). Like reports in human studies (Phillips et al., 2017), reports of thermal allodynia in animal models of OA is scarce (Lee et al., 2009). Allodynia (pain due to a stimulus that does not usually provoke pain) is a prominent symptom in individuals with neuropathic pain, and can be triggered by physical stimuli to the affected site.

A proportion of participants also provided discussions surrounding the theme of 'weather induced pain'. Many individuals with joint pain believe that factors such as ambient temperature, barometric pressure, relative humidity, sunshine, wind speed and precipitation, which are related to weather have influence joint pain (Quick, 1997; Wilder et al., 2003). While the relationship between weather and knee pain has been explored qualitatively within the literature (Nio Ong et al., 2011; Selfe et al., 2010), studies aimed at quantifying the relationship between weather temperatures and joint pain are scarce, vulnerable to bias, and inconsistent (Laborde et al., 1986; McAlindon et al., 2007; Strusberg et al., 2002; Wilder et al., 2003)

Thermotherapy (the therapeutic application of any substance to the body that adds heat to the body resulting in increased temperature) was also discussed in relation to the neuropathic-like pain item. While no studies have investigated the therapeutic role of heat therapy in knee OA, one systematic review has shown that application of ice packs did not affect pain significantly in patients with OA pain, compared to controls (Brosseau et al., 2003). Rewriting this neuropathic-like pain item ensured that all the participant interpretation for this item was specific to the theme of thermal allodynia. The revised version of the neuropathic-like pain item was found to work well in a second round of interviews, and was retained in the final version of the CAP-Knee questionnaire (Appendix 13.11, *p397*).

Majority of the response problems identified following content analysis of the CAP-Knee items were also due to poor performance of items representing fatigue and cognitive impact. These items were however not considered for revision because every theme surrounding participants discussions for these

items aligned with the intended interpretation. The fatigue themes discussed here are consistent with one study showed that fatigue is associated with physically strenuous work and comorbid clinical conditions such as diabetes and fibromyalgia, and sleep disturbance (Åkerstedt et al., 2002). Participants in this study discussed relief from fatigue by taking rest periods during the day, which is consistent with behavioural prescriptions (≤30 minutes at a time) provided to individuals with chronic fatigue syndrome (Friedberg & Krupp, 1994). However, such rest periods have been shown to reduce sleep quality and quantity in healthy individuals (Paech et al., 2014). Future work should definitively explore the benefit of such behavioural prescriptions on sleep quality within individuals with chronic knee pain who also report fatigue symptoms.

A main theme of task distraction was highlighted by participants during discussions about the item which represented cognitive impact. This theme is synonymous with the “interruptive function of pain” phenomenon (Eccleston & Crombez, 1999). Impaired performance on attentional demanding tasks have previously been reported in individuals with chronic pain (Eccleston, 1994; Eccleston, 1995; Kuhajda et al., 2002). This finding is in line with the notion that pain imposes a high and overriding priority on an action-oriented attentional system, because of the evolutionarily importance of pain to signal harm and the urge to escape. Somatic awareness, also highlighted during discussion related to the cognitive impact item, has previously been identified in individuals with chronic pain, and is described as the extent to which an individual reports the perception of bodily sensations (Eccleston et al., 1997).Somatic awareness was found to be greater in individuals with widespread pain conditions such as fibromyalgia, compared to individuals with a more localised pain conditions such as lower back pain and other musculoskeletal pain (Dick et al., 2002). Together, these items representing cognitive impact and fatigue did not meet the criteria for item revision and were retained in the final version of the CAP-Knee as initially worded in the original version of the CAP-Knee.

Although the literature is scarce, previous studies have suggested that the process by which chronic pain predicts depression involves both disrupted social- functioning (Gayman et al., 2008; Sturgeon et al., 2015). While the theme of physical limitation emerging from discussions around the depression

item was not in keeping with the intended interpretation, only a small proportion (9%) of individuals provided responses related to codes of poor item function. Thus, this item did not meet the criteria for item revision and was retained in the final version of the CAP-Knee as initially worded in the original version.

Discussions surrounding items representing anxiety, pain distribution, catastrophizing and sleep were in keeping with the intended interpretation of the items, and were found to work well following content analyses, with <10% of participants providing responses related to codes of poor item function.

As described in the literature, anxiety has been linked to fear for individuals with chronic illnesses (Halpin et al., 2015), including chronic pain (Asmundson & Katz, 2009). The participants described an overall theme of fear whilst discussing the anxiety item, interpreted as fear related to the affected knee (i.e. damage within the affected knee), fear related to the individual's future, as well as a fear of falling over. A fear of falling over has been described in previous work to be present in older adults with chronic musculoskeletal pain (Nyvang et al., 2016; Stubbs et al., 2014). Participants left fearful of damage to the affected site has also been described in back pain populations (Bunzli et al., 2015; Stenberg et al., 2014).

Discussions surrounding the item representing catastrophizing in the current study revolved around themes of hypervigilance, and beliefs surrounding causes and consequences of the knee pain experienced by the study participants. One study previously showed that vigilance to pain was greater in individuals with centralized pain conditions such as fibromyalgia, compared to individuals with a more localised pain condition such as lower back pain (Crombez et al., 2004). Thus, it is possible that pain vigilance might be present in higher levels in cases where central mechanisms are present in individuals with OA knee pain. Pain vigilance identified correlates significantly with pain intensity and catastrophic thinking about pain (Crombez et al., 2004; Schütze et al., 2010). Beliefs, such as causes and consequences of pain have previously been shown to associate significantly with catastrophizing in a previous study (Sloan et al., 2008). Catastrophizing has previously been shown to associate with persistent pain following total knee replacement, a clinical marker of central pain mechanisms (Drosos et al., 2015; Edwards et

al., 2009). Thus, addressing beliefs linked to maladaptive coping techniques in clinical practice, including catastrophic thinking, might be beneficial for the reduction of pain intensity in individuals with centrally mediated knee pain.

The relationship between sleep and pain has been explored within the literature. Previous authors have described that OA-related knee pain was related to sleep disturbance in cross sectional and longitudinal studies (Parmelee et al., 2015; Wilcox et al., 2000). Participants' discussions surrounding the pain distribution item revolved around the painful sites they experienced, the nature of pain they experienced, the perceived impact of the pain experience, and help-seeking experience. This theme of the nature of pain experienced by participants, is in keeping with use of the pain manikin to capture qualities of pain in individuals with back pain (Uden et al., 1988).

Clinical examination showed that majority of the participants recruited to this study had evidence of knee OA present within one or both knees. It should be emphasized that in this study sample, knee pain was differentiated from inflammatory pain (e.g. rheumatoid arthritis) during participant recruitment, and in contrast to acute pain, pain had been present for most days of the preceding month. This study was undertaken only within the Nottinghamshire region of the UK, and the findings may not be nationally or globally transferable.

This study had its limitations. Although assessment of intercoder reliability during the content analysis process sought to reduce researcher bias, it is possible that the study findings may have been influenced by the researcher bias inherent during the categorization of themes. Rigour is often difficult to achieve during thematic analysis (Nowell et al., 2017). In order to maintain rigour during thematic analysis, the study team held frequent discussions about emerging themes and associated quotes in order to come to consensus on the themes and deciding on whether or not themes were aligned to the intended interpretation.

Saturation within the current study was achieved using data from a total of 22 participants, with interviews conducted across multiple rounds. Little research has been conducted on how many interviews are needed to identify all problems in cognitive operations. While some issues might not be identified

until sample sizes of 50 or more are interviewed, there is evidence that small numbers of cognitive interviews expose proportionally more serious problems than minor issues (Blair & Conrad, 2011). Recommendations for sample sizes during cognitive interviews are typically low, ranging from 5 for a single round, and 15 across multiple rounds (Beatty & Willis, 2007; Willis, 2005).

Overall, the qualitative evidence collected during this study demonstrates that seven of the eight original items representing traits of anxiety, depression, catastrophizing, cognitive impact, sleep, fatigue, and pain distribution included within the CAP-Knee questionnaire, as well as the revised neuropathic-like pain item, are consistently interpreted as intended, thus substantiating the content validity of this new measure (Patrick et al., 2011).

8.2.5. The CAP-Knee Questionnaire: A psychometric evaluation.

The need for psychometrically sound assessment instruments in clinical and research practice is continuously reinforced in the literature (Boateng et al., 2018). Using Rasch and traditional psychometric approaches (Wright, 1996), this study confirmed the unidimensionality of the 8-item CAP-Knee questionnaire. In keeping with the Rasch assumption of local independence, no evidence of response dependency and multidimensionality was found (Baghaei, 2008; Pallant & Tennant, 2007; Tennant et al., 2011). Improvement of the summary statistics for the items following item rescoring supports use of the 8-item model with collapsed response categories. The Rasch transformed scores for the revised scoring model performed just as well as the true population scores in CFA and reliability analyses, supporting use of the revised scoring of 8-item questionnaire.

Future work is needed to address other clinical properties of the CAP-Knee: including (i) distinguishing between subjects based on the presence of centrally augmented knee OA pain; (ii) predicting the results of a concurrent or future gold standard measure; and (iii) measuring change within subjects over time. The CAP-Knee primarily seeks to identify subgroups of individuals with augmented central mechanisms driving knee OA pain. To compare results from one subgroup to another, the CAP-Knee must be shown to measure the same thing across the knee OA pain population, for which it was designed. CFA approaches confirmed the hypothesized one-factor structure supporting the findings in previous chapters (Chapter 4 and 5), where 8 different self-

report traits contribute to one unifying trait, termed ‘Central Mechanisms’. However, further assessment is warranted, to demonstrate sensitivity and specificity of the CAP-Knee as a classification tool that identifies subgroups of individuals with centrally augmented OA pain.

A Rasch conversion table for the 8-item model following rescoring of the response categories is provided to aid longitudinal tracking of the Central Mechanisms trait, or for use as an outcome measure during parametric analyses. These interval level scores will therefore support accurate longitudinal monitoring that could inform future clinical care and research. It is generally accepted that once reliability and validity have been established, an otherwise appropriate test is ready for use as an outcome measure in clinical trials. Outcome measures should however also be able to detect therapeutic responsiveness by measuring change over time, With respect to clinical trials, responsiveness has also referred to the ability of a measure to distinguish between treatments, in particular, between an active/experimental treatment and a placebo/control treatment. To determine responsiveness, the minimal clinically important differences (MCID) and minimum detectable change (MDC) can be calculated using change scores. Future work is needed to assess CAP-Knee clinometric properties in other to judge whether treatments have resulted in real change and the magnitude of the benefit of interventions (Wright., 1996).

While previously existing questionnaires, such as the CSI-9 has been identified to fit the Rasch model, the CSI-9 showed multidimensionality according to Rasch and CFA models (Nishigami et al., 2018). It is however important to note that unidimensionality is not an absolute but a relative matter and there is no single agreed upon method to test for unidimensionality. While the GPQ seeks to measure symptoms that are prevalent in individuals with fibromyalgia (van Bemmel, Voshaar, Ten Klooster, Vonkeman, & van de Laar, 2019), both the GPQ and CSI-9 did not include several items included in the CAP-Knee scale, such as the neuropathic-like pain and cognitive impact item, which have been shown here to associate with a QST marker of central mechanisms in individuals with knee pain (Chapter 4).

Misfit between the Rasch model and the data was observed, which was due to the pain distribution item which showed uniform DIF for age, and due to misfit

of the cognitive impact item. The Rasch analysis also demonstrated that respondents had trouble distinguishing between response categories, specifically between ‘often’ and ‘always’. Thus, the probability that persons with similar levels of central pain mechanisms would choose one description over another was not predictable. This supports findings from the qualitative study (Chapter 6.5.3) which demonstrated that 59% of individuals experienced uncertain initial response to at least one item included within the CAP-Knee. Based on this, further research seeking to develop other versions of the CAP-Knee targeted towards other localized joints, might benefit from collapsing the last two response categories for the first seven items, as reported in this study.

Exclusion of the misfitting cognitive impact and pain distribution items from the model, and collapsing the response categories for the remaining items achieved better fit to the Rasch model. This suggests that the two excluded items may not be as important when tracking the Central Mechanisms trait as an outcome measure. However, the decision on whether the CAP-Knee should be implemented as either an 8-item, or a 6-item tool should ultimately come from outside the data and clinical/theoretical considerations from previous chapters support the inclusion of these items within the questionnaire (Andrich, 1988).

Rasch analyses conducted in sample sizes such as that employed in this study (n≥250) leads to even minor levels of misfit being statistically significant when chi-square statistics are used (Chen et al., 2014a). In essence, there is a risk that a larger sample size is powered to find very small differences, making the target of a non-significant chi-square value for item-trait interaction increasingly stringent.

The current study findings support the item loading patterns previously identified, with the cognitive impact item showing the strongest loading to the underlying latent trait, and the pain distribution items showing the weakest loading. The weak loading of the pain distribution item to the identified latent trait suggests that it could possibly contribute to its own factor. Widespread pain distribution has previously been shown to associate with suggest altered pain processing in the CNS (Croft et al., 2005; Graven-Nielsen & Arendt-Nielsen, 2002; Gwilym et al., 2009). Future studies should seek to identify the exact role that pain distribution plays in the pathway between localization pain

and centrally augmented pain. Previous work in the larger KPIC cohort (chapter 5) demonstrated relationships between the pain distribution item and items measuring each of the other seven traits measured in the CAP-Knee. Similar correlations were observed between the pain distribution item and the neuropathic-like symptoms item, in both the CAP-Knee study and KPIC study population. However, the magnitude of the relationship between the pain distribution item and the items representing depression, catastrophizing and cognitive impact item were substantially smaller in the CAP-Knee study population, compared to the KPIC study population. This might be due to population differences between both cohorts, however, these findings should ultimately be confirmed using larger scale studies.

The CAP-Knee was also shown to be reliable across participants, and across time points, supporting the application of the CAP-Knee in assessing central mechanisms trait in individuals with knee pain over different sessions. This finding is similar to other central pain mechanisms measurement approaches, including imaging (Letzen, Boissoneault, Sevel, & Robinson, 2016), QST (Kong, Johnson, Balise, & Mackey, 2013) or self-report approaches (Nishigami et al., 2018).

There were potential elements of bias that may have been introduced during the study. The traits assessed within the CAP-Knee may not constitute an exhaustive list of traits related to Central Mechanisms. The repeatability period employed in this study ranged from across a couple of days to one moth intervals, and future work will benefit from establishing whether the time lag between questionnaire completion influences the repeatability of the CAP-Knee. In general, higher reliability is found within shorter time spans due to the fluctuation of pain itself (Jensen, 2003). In addition, the study population employed in this study was based on a community sample recruited via primary care. It is possible that individuals recruited from secondary care settings may respond differently to the CAP-Knee. Participants also completed the CAP-Knee at home, and the psychometric properties reported in this study might have be influenced should participants complete the questionnaire within clinical settings. Future work might benefit from exploring how these settings influenced the current study findings.

8.3. Novel findings and implications

This study is the first to show that distinct psychological and somatic self-report traits demonstrated to influence knee pain all contribute to a unifying latent trait, deemed in this project to reflect “central mechanisms”. This finding that 8 items representing 8 different traits contributed to one unidimensional trait was consistent across the project, and is supported by previous studies assessing similar traits measured within the CAP-Knee (van Bemmel et al., 2019). The CAP-Knee showed good psychometric performance, supporting its use as a mechanism based tool within clinical and research settings. Unlike the CAP-Knee items, other questionnaires developed to assess symptoms liked to CS, such as CSI-9 and GPQ (Nishigami et al., 2018; van Bemmel et al., 2019), did not include several items included in the CAP-Knee scale, (*such as the cognitive impact- and neuropathic-like pain items*). The items selected for inclusion within the CAP-Knee were shown to associate with a QST marker of central mechanisms (Chapter 4), thus demonstrating external validity for the selected items, and for the Central Mechanisms trait.

Previous studies have shown that the reported number of painful sites are associated with knee pain severity (Croft et al., 2005), and that widespread pain distribution, a key feature demonstrated in individuals with fibromyalgia, is linked to augmented central mechanisms (Graven-Nielsen & Arendt-Nielsen, 2010). However, associations between the body pain manikin and QST measures of CS in individuals with knee pain, or use of the manikin in identifying individuals with centrally augmented pain, were first identified in this thesis. Thesis findings of poor sensitivity, poor AUC and weak correlation between the manikin and PPT values across all sites, suggest that the body pain manikin may not be discrete enough a measure to classify PPT features of centrally augmented knee OA pain by itself. This finding therefore supports the overall thesis notion that inclusion of the pain distribution trait alongside other traits linked to central mechanisms, within a composite tool, might improve the performance of self-report measures in classifying individuals with centrally augmented pain.

This project not only showed that the Central Mechanisms trait is a good measure for identifying individuals who are more likely to report pain resolution or pain persistence at follow-up, but supports the notions that the prognostic

characteristic of a measure of peripheral mechanisms (*e.g. radiographic disease severity*), would improve if the Central Mechanisms trait is also considered (Chapter 5). No self-report measures linked to underlying peripheral knee pain mechanisms were identified in this study. However, there is potential that combined administration of self-report measures linked to both peripheral and central knee pain mechanisms would be useful in clinical and research settings to identify individuals who might show poor prognosis at follow-up time points.

The qualitative study conducted within this project is the first of its kind to explore individual's interpretation of items representing traits typically assessed in a knee pain population. This finding not only adds validity to the items included within the CAP-Knee, but provides a rich source of information to other researchers seeking validated self-report items measuring specific traits for use within a knee pain population.

While some of the ESEM findings in this thesis are similar to those identified in other chronic pain populations, researchers must be careful not to depend on the factor structures identified within a different clinical population, especially when generalizability of the factor structure to the relevant clinical population is yet to be demonstrated (Reise, Waller, & Comrey, 2000). The ESEM findings in this thesis are the first within the knee pain population to assess factor structure of questionnaires assessing traits relevant to the knee pain experience. Thus, the ESEM findings within the current project adds validity to the use of these questionnaires (*including the HADS, PCS and mPDQ*) within a knee pain population.

8.4. Future research

Primary care physicians can often see 20 to 30 patients per day in 15-minute sessions (Lehnert & Bree, 2010), and are particularly challenged with achieving clinically important pain relief in a subgroup of patients with knee OA pain, following treatment. Tools to select interventions for patients with knee OA pain, are not widely available for widespread use in clinical practice, especially in primary care settings, such as GP practices. Clinical decision support tools are another strategy used throughout the health care system to assist clinicians in decision making, often specifically in diagnosis and assessment (Forseen & Corey, 2012). Such tools have potential to greatly

enhance a clinician's ability to carefully subgroup patients, and inform mechanism-based treatment allocation (Gross et al., 2016; Kosinski, 2013).

Self-rating scales have become increasingly popular in assessment of various dimensions of pain. They have proved to be applicable for screening in epidemiologic studies, for recognition of the underlying trait, and for the assessment of change following treatment. A one-size-fits-all primary care strategy is suboptimum because it ignores the heterogeneity seen within the knee pain population. While QST and imaging approaches might help achieve mechanism-based subgrouping in clinical and research settings, their administration is time-consuming and requires specific training. Self-report approaches also have an advantage in speed and ease of administration The CAP-Knee was therefore developed in this project as a mechanism-based subgrouping tool to aid treatment decisions across individuals with knee OA pain. This idea is reflected in the selected self-report items which were demonstrated to show an association with a QST measure of central mechanisms (Chapter 4).

Details of future work proposed to further validate the CAP-Knee as a measure of central mechanisms are outlined below:

8.4.1. Defining cut-off points

By demonstrating the psychometric properties, the CAP-Knee can be used not only as a dimensional measure, but also for classification of subgroups with centrally augmented knee OA pain.

To influence evidence-based guideline recommendations and to utilize the CAP-Knee scale in research and clinical settings, interpretation of CAP-Knee scores needs to be easier. Continuous absolute and change scores for each respondent must be converted into a dichotomous variable. An absolute value below a clinically relevant cut-off is needed to define clinically important levels of central pain augmentation. It is also important to define a clinically relevant cut-off defining an important change from the patient's perspective.

The next steps for CAP-Knee development should seek to determine binary cut-off points that identify subgroups of individuals reporting centrally augmented pain. Longitudinal work should determine cut-off points for baseline CAP-Knee scores predicting future pain outcomes. In addition,

longitudinal work aimed at identifying mediators or moderators of the relationship between CAP-Knee scores, and future pain prognosis, would shed some light on the specific treatment pathways that can influence individualised treatment pathways.

8.4.2. Randomized Control Trials (RCTs)

Findings within the thesis have provided evidence on the predictive potential of the newly developed tool, which has shown internally valid, reliable and acceptable questionnaire to inform appropriate decisions on treatment of knee OA pain. Future research will test external validity of the tool in other settings (particularly in primary care settings), to evaluate implementation, and study the impact of the tool on patient and health services outcomes. Such work will benefit from end-user engagement in order to ensure its usefulness and positive impact on clinical practice (Hayden et al., 2019).

The CAP-Knee may show clinical utility within a primary care setting when applied within a knee pain population. For example, in comparison to a non-stratified treatment approach in a back-pain population, a stratified approach using a self-report tool, has been shown to provide clinical- and cost-effectiveness (Hill et al., 2011). RCTs should further investigate whether a stratified treatment approach using the CAP-Knee, will result in clinical and economic benefits, compared with current best practice.

8.4.3. Identifying modifiable traits

RCTs can also assess the clinical benefits of addressing modifiable mediators/moderators in CAP-Knee high scorers compared to low scorers. This study will explore responsiveness of individuals with knee pain to novel, complex or repurposed pharmacological and non-pharmacological therapies targeted to relevant traits identified in the current work.

There is a gap in the cause and effect relationship between central mechanisms and pain outcomes. For example, it is difficult to unequivocally ascertain whether the presence of central mechanisms leads to persistent knee OA pain, or whether knee OA pain can lead to higher incidences of central mechanisms. Well powered longitudinal studies for response to mechanism-based treatments, with long follow-up periods, will be beneficial

for assessing the treatment and individual trajectories within the heterogenous knee pain population.

It is likely that the effect of baseline measures of central mechanisms (*as indicated by increased CAP-Knee scores*), on pain intensity at follow-up, might be due to changes in a combination of modifiable traits measured within the CAP-Knee. Therefore, employing more sophisticated treatment approaches such as a combination of anti-neuropathic treatments and cognitive behavioural therapy, might be more effective than usual or minimal care of knee pain. Longitudinal research might also explore whether traits, or the latent Central Mechanisms trait identified in the current study, might predict treatment response to centrally targeted treatments.

8.4.4. CAP-Knee generalizability

Future work should seek to develop and validate a generalizable version of the CAP-Knee which can be utilized in the identification of individuals with central mechanisms across other localized musculoskeletal pain conditions. Such a tool has potential to show clinical utility in mechanism-based treatment stratification across a variety of conditions where there is potential for central pain augmentation. In addition, a central mechanisms-based tool would not only show utility within musculoskeletal pain (e.g. in individuals with RA), but might also be beneficial for screening individuals in surgical populations to determine those who might be predisposed to chronic post-surgical pain due to underlying central mechanisms (Correll, 2017; Searle & Simpson, 2009; van Helmond, Steegers, Filippini-de Moor, Vissers, & Wilder-Smith, 2016). However, it is currently unknown whether all central mechanisms are shared between all chronic pain conditions, and the performance of items might differ between people with primary centralized pain problems (e.g. Fibromyalgia), and those with central augmentation of arthritis pain.

8.4.5. Other future work

Findings from this project suggests that the central mechanisms trait measured within the CAP-Knee might predict pain intensity across individuals with knee OA pain. Findings from Chapter 4 and 5 demonstrates that the Central Mechanisms traits (as measured by single items included within the KPIC survey) is moderately associated with baseline and future pain intensity, independent of radiographic severity. These findings are yet to be reproduced

using the final version of the CAP-Knee, but suggests that the Central Mechanisms trait and pain intensity are two separate constructs (thus demonstrating divergent/discriminant validity, where measurements that are not supposed to be related are actually unrelated). Thus, using multiple regression models, future work can determine whether the CAP-Knee score for the central mechanisms trait predicts treatment outcomes, independent of pain severity.

Chapter 4 also demonstrated a lack of association between the Central Mechanisms trait traits (as measured by single items included within the KPIC survey) and radiographic scores, suggesting divergent/discriminant validity. This finding suggests that while these measures of peripheral and central mechanisms are distinct from each other. Future work is needed however to validate these findings using the CAP-Knee score for the Central Mechanisms trait. Cross sectional work could conduct CFA to determine whether radiographic severity contributes to the latent trait measured within the CAP-Knee. Tests for associations between the CAP-Knee and radiographic scores in an external knee pain population might further verify whether or not both CAP-Knee and radiographic scores measure distinct knee OA pain mechanisms.

Further studies aimed at demonstrating associations between CAP-Knee scores and other self-report, imaging or psychophysical markers of central mechanisms would be useful in establishing concurrent validity of the CAP-Knee with other measures of central knee pain mechanisms.

8.5. Conclusion

In summary, key findings from the studies undertaken for this thesis are as follows:

1. Eight items representing psychological and somatic self-report traits show content validity for measuring traits linked to central mechanisms of knee pain, and these items show significant associations with a psychophysical marker of central mechanisms.
2. Eight items representing eight respective psychological and somatic self-report traits measure a single underlying latent trait, termed ‘Central Mechanisms’, which shows significant associations with a

psychophysical marker of central mechanisms, and baseline pain, irrespective of demographic or radiographic factors.

3. After accounting for demographic variables, radiographic scores, and symptom duration, increasing for the Central Mechanisms trait scores are associated with an increased risk of pain persistence, and with persistent pain severity scores. The Central Mechanisms trait scores also shows good prognostic characteristics for discriminating between individuals reporting pain persistence and resolution at 1-year follow-up.
4. The final version of the CAP-Knee consisted of rewritten and standardised versions of the selected eight self-report items which contribute to the Central Mechanisms trait. Interpretation of these items by individuals with knee pain were aligned with intended item meanings, supporting content validity of the rewritten items.
5. The CAP-Knee scale showed good psychometric properties, including unidimensionality, internal consistency and test retest reliability, within a knee pain population.

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APPENDICES

Appendix 1. KPIC baseline survey.

Nottingham University Hospitals NHS
NHS Trust

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Q - 001

Knee Pain and Related Health

Knee pain, often due to osteoarthritis, is a very common problem affecting 1 in 4 people over the age of 40. We want to understand why some people are more affected than others and the risk factors and health problems associated with knee pain. We would therefore be very grateful if you would take the time to complete this questionnaire, **regardless of whether or not you have knee pain**. We hope you find it interesting. It takes approximately 30 minutes to complete. Most of the questions just require a tick in a box, but for others, clear instructions are given.

We would also be grateful if you could confirm, on the last page of the questionnaire, whether you would be willing to complete a follow-up questionnaire in approximately one years' time and also whether you would like to receive information about further research which will involve a single visit to the Nottingham City Hospital, clinical assessments and an x-ray.

Please return this questionnaire, in the pre-paid envelope **(no stamp required)** to Academic Rheumatology at the Nottingham City Hospital as soon as possible.

Your answers are strictly confidential

If you have any questions or require any assistance completing the questionnaire please telephone: Nadia Frowd on 0115-8231676

Thank you for your assistance with this important area of research.

Chief Investigator – Professor Michael Doherty

Approved by: Nottingham 2 Research Ethics Committee

Funded by: Arthritis Research UK
Providing answers today and tomorrow

Version 2.1, Date:7.5.14

Office use only SURGERY ID

SECTION 1 – About Yourself

1. What is your Date of Birth?

   [D][D] Day [M][M] Month [Y][Y][Y][Y] Year

2. What Sex are you?

   ☐ Male ☐ Female

3. What is your Height? *Please complete one box only*

   ☐ Feet ☐☐ inches **OR** ☐☐☐ centimetres

4. What is your Weight? *Please complete one box only*

   ☐☐ stones ☐☐ pounds **OR** ☐☐☐ kilograms

year 3.

5. Please can you list all **main occupations** you have had, state whether the occupation was full time (F) or part time (P)* and the number of years spent in each occupation.

List of Occupations	Full time (F) or Part time (P)	Time Period *(e.g. 3 years)*
1)		
2)		
3)		
4)		
5)		
6)		
7)		

***Full time:** More than 20 hours per week
Part time: 20 hours or less per week

1

SECTION 2: About Your Medical History and Medication

6. Have you **ever** been diagnosed by your doctor as having any of the following?

- ☐ High Cholesterol
- ☐ Diabetes
- ☐ Heart Attack / Angina
- ☐ Stroke
- ☐ Hypertension / High Blood Pressure
- ☐ Irritable Bowel Syndrome
- ☐ Osteoarthritis of the Hip
- ☐ Fibromyalgia
- ☐ Osteoarthritis of the Knee
- ☐ Chronic Fatigue Syndrome
- ☐ Cancer *Type:* _____

Other medical conditions not listed above: _____

_____

7. Have you broken either of your legs **in the last 10 years**?

☐ Yes ☐ No

If yes, at what age did this break occur? _____ *years old*

If yes, which bone did you break? _____

8. Have you **ever** suffered significant injury to either of your knees?

☐ Yes, *please specify:* _____ ☐ No

If yes, did this knee injury require that you see a doctor or go to a hospital for treatment?

☐ Yes ☐ No

9. Please list **all** your **current medication** including those **prescribed by your doctor** and those you **bought yourself** over the counter (*please* ***include any hormonal medication*** *such as oestrogen supplements,* ***vitamin supplements and alternative medicines****) Please indicate the approximate number of months or years you have taken each of these.*

Name of Medication	Duration	
	Years	Months
1)		
2)		
3)		
4)		
5)		
6)		
7)		
8)		
9)		
10)		

10. Have you ever taken any **"statins"** medications for lowering your cholesterol and lipids? Examples of statins are Atorvastatin (also known as Lipitor), Simvastatin (also known as Zocor), and Rosuvastatin (also known as Crestor)

Are you still taking a statin?

☐ Yes ☐ No

For approximately how many years have you taken a statin? _____ *years*

3

SECTION 3: About Your Knee Pain

11. Have you **ever** had pain in or around a knee on most days for **at least a month**?

☐ Yes ☐ No ***(if No, please go to Section 4)***

If yes, at what age did you first notice this type of knee pain? _____ *years old*

12. Have you had knee pain on most days of **this past month**?

☐ Yes ☐ No

13. Has your current knee pain lasted **more than 3 months**?

☐ Yes ☐ No

14. Since it has started, do you think the severity of your knee pain has overall...

☐ Greatly Improved ☐ Slightly Improved ☐ Remained the Same ☑ Worsened

15. Which knee(s) do you / did you experience the pain in?

☐ Right ☐ Left ☐ Both

If both, which overall is the worst knee?

☐ Right ☐ Left ☐ Equal

16. Have you ever had any injections into your knee?

☐ Yes ☐ No

17. If you answered "**yes**", was it:

☐ Steroid Injection ☐ Hyaluronic Acid Injection ☐ Don't Know

4

18. Have you **ever** had an operation on either of your knees?

☐ Yes ☐ No

If yes, what type of operation did you undergo? *(If you did not undergo one of the specific operations then please leave the related boxes blank)*

Type of Operation	Which Knee? (Right, Left, Both?)	Age at Time of Operation *(years)*
Arthroscopy / Telescope / Keyhole		
Ligament Repair		
Meniscus or Cartilage Removal		
Joint Replacement		
Other, *please specify* _____		

2 week baseline data.

19. Have you **ever** consulted a healthcare professional (eg your GP, a hospital specialist, a physiotherapist etc) about your knee pain?

In the past 12mo

☐ Yes ☐ No

20. Approximately how many different things have you tried for your knee pain (including things like drugs, exercise, changes to diet, footwear modifications etc)? Please include <u>everything</u> you have tried, regardless of whether or not it was recommended by a healthcare professional.

In the past 12 mo

☐

21. Which of the various things you have tried has helped your knee pain the most?

_____

5

22. **The following questions are to be answered by people who have knee pain.**

We want you to tell us about the knee **where you have the greatest pain**. To get a better sense of the different types of knee pain you may experience, we would like to ask you about any "constant pain" (pain you have all the time) separately from any pain that you may experience less often, that is "intermittent" (pain that comes and goes).

We appreciate that some of these questions may seem a bit repetitive but they have been shown to provide important information about knee pain. **Please answer ALL the questions**.

9COAP

For each of the following questions please select the answer that best describes **on average your <u>constant knee pain</u> in the PAST WEEK.**

	Not at all	Mildly	Moderately	Severely	Extremely
a. In the past week, how intense has your CONSTANT KNEE PAIN been?	☐	☐	☐	☐	☐
b. In the past week, how much has your CONSTANT KNEE PAIN affected your sleep?	☐	☐	☐	☐	☐
c. In the past week, how much has your CONSTANT KNEE PAIN affected your overall quality of life?	☐	☐	☐	☐	☐
d. In the past week, how frustrated or annoyed have you been by your CONSTANT KNEE PAIN?	☐	☐	☐	☐	☐
e. In the past week, how upset or worried have you been by your CONSTANT KNEE PAIN?	☐	☐	☐	☐	☐

6

23. Now please select the response that best describes **on average your knee pain that comes and goes in the PAST WEEK**

	Not at all	Mildly	Moderately	Severely	Extremely
a. In the past week, how intense has your **knee pain that comes and goes** been?	☐	☐	☐	☐	☐
b. In the past week, how much has your **knee pain that comes and goes** affected your sleep?	☐	☐	☐	☐	☐
c. In the past week, how much has your **knee pain that comes and goes** affected your overall quality of life?	☐	☐	☐	☐	☐
d. In the past week, how frustrated or annoyed have you been by your **knee pain that comes and goes**?	☐	☐	☐	☐	☐
e. In the past week, how upset or worried have you been by your **knee pain that comes and goes**?	☐	☐	☐	☐	☐
f. In the past week, how frequently has this **knee pain that comes and goes** occurred?	☐	☐	☐	☐	☐

7

We now want to ask you about **any kind of knee pain** that you may be currently experiencing

24. **Over the past month**, in your most painful knee, does pain **run up or down** your leg?

☐ Yes ☐ No

Please tell us about the **intensity of discomfort** you experience in or around your **most painful knee.**

25. How would you rate your most painful knee pain on a 0-10 scale at the present time, that is **right now**, where 0 is 'no pain' and 10 is 'pain as bad as could be'? (Please circle only ONE number)

No Pain										**Pain as bad as it could be**
0	1	2	3	4	5	6	7	8	9	10

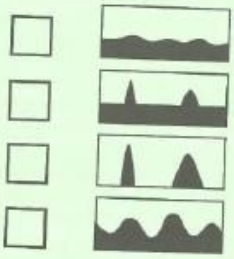
26. In the **past month**, how intense was your **'worst knee pain'** rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'?
(Circle only ONE number)

No Pain										**Pain as bad as it could be**
0	1	2	3	4	5	6	7	8	9	10

27. In the **past month**, on **average**, how **intense** was the pain in your **most painful knee** rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'? (That is, your usual pain at times you were experiencing pain.) (Circle only ONE number)

No Pain										**Pain as bad as it could be**
0	1	2	3	4	5	6	7	8	9	10

28. This next question is on the pattern of your pain in your **most painful knee.** Which of the 4 different options below is the one that best describes the pattern of your worst knee pain over the past month? (Tick one box)



☐ Persistent pain with slight fluctuations

☐ Persistent pain with pain attacks

☐ Pain attacks without pain between them

☐ Pain attacks with pain between them

29. Please select the response that best describes the **type of pain in your most painful** knee over the **past month**. Please do not leave any questions blank and tick one box.

	Never	Hardly Noticed	Slightly	Moderate	Strongly	Very Strongly
a. Do you suffer from a burning sensation (eg stinging nettles) in or around your most painful knee?	☐	☐	☐	☐	☐	☐
b. Do you have a tingling or prickling sensation in the area of your most painful knee 'pain' (eg like crawling ants or electrical tingling?)	☐	☐	☐	☐	☐	☐
c. Is light touching (clothing, a blanket) in this area painful?	☐	☐	☐	☐	☐	☐
d. Do you have sudden pain attacks in the area of your most painful knee 'pain', like electrical shocks?	☐	☐	☐	☐	☐	☐
e. Is cold or heat (bath water) in this area occasionally painful?	☐	☐	☐	☐	☐	☐
f. Do you suffer from a sensation of numbness in or around your most painful knee?	☐	☐	☐	☐	☐	☐
g. Does slight pressure in this area, (e.g. with a finger), trigger pain?	☐	☐	☐	☐	☐	☐

9

OUT

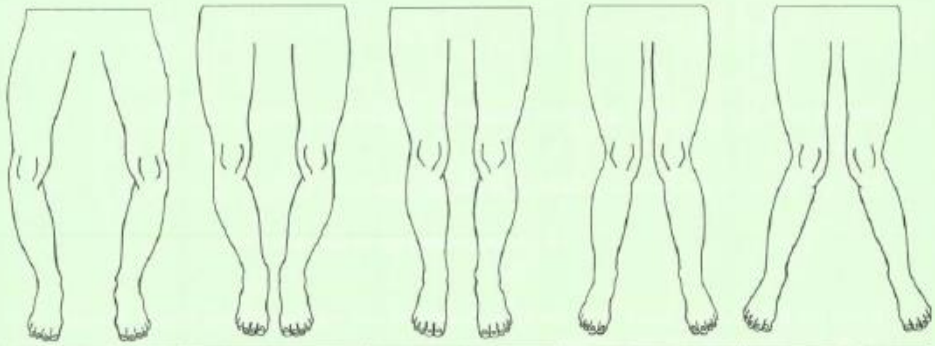
SECTION 4: About the Angle of your Legs

30. We are interested in the angle of your legs (that is, straight legs, bow-legged or knock knees) as this may have relevance to the development of osteoarthritis.

del

Please look at your legs **whilst standing** (preferably in front of a mirror) and then indicate the angle of your legs based on the diagrams below.

Most people will have similar angulations in their left and right knees, but in a few people these angulations may differ. We therefore would like you to score your knees separately.



A	B	C	D	E
Very bow legged	Bow legged	Straight	Knocked-knee	Very knocked-knee

a) Which diagram best shows the **current** angle of **each** of your legs?

Right Leg	☐ A	☐ B	☐ C	☐ D	☐ E
Left Leg	☐ A	☐ B	☐ C	☐ D	☐ E

b) Which diagram do **you think** best shows the angle of **each** of your legs **in your 20s**?

Right Leg	☐ A	☐ B	☐ C	☐ D	☐ E
Left Leg	☐ A	☐ B	☐ C	☐ D	☐ E

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SECTION 5: About Your Hands

We are interested in knowing whether you have any finger nodes. These sometimes relate to arthritis in the hand and other joints.

A finger **node** is a firm, bobbly swelling on the back of the finger joint. They look like the examples below:

A finger **without** nodes:

A finger **with** nodes:

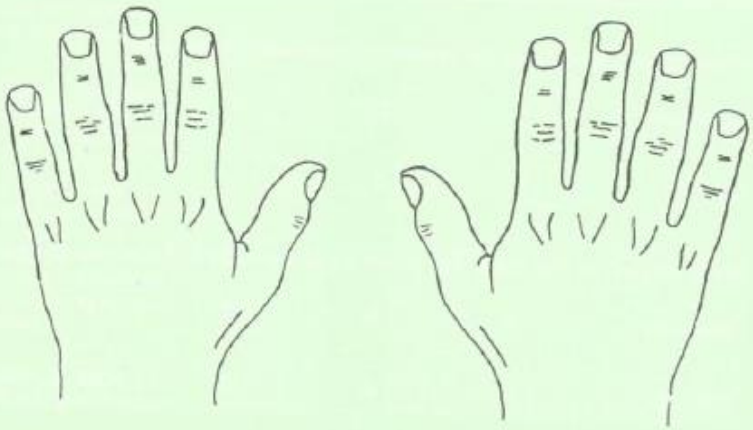
Please look at your hands and then answer the following questions

31. Do you think you have any **nodes/swellings** on your hands?

☐ Yes ☐ No ***(if No, please go to Question 32)***

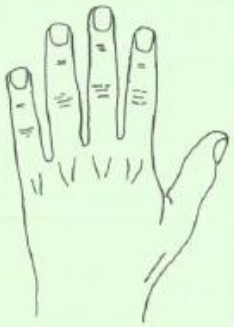
If yes, for each hand please circle the finger joint(s) where you have these nodes. *Please circle ALL the joints that are affected*

LEFT **RIGHT**



32. We are now interested in which of your **index** and **ring** fingers is longer. **First,** please look at one of your hands with your **fingers straight in line with your forearm.** If you have arthritis in the hands please look at the hand with less arthritis.

Ignore your middle finger and try to **focus only on your index and ring fingers.** Select from the pictures below the one that best shows the length of your **index finger** in comparison to your **ring finger** and tick the appropriate box.

Index finger longer than ring finger	**Both fingers are of equal length**	**Ring finger is longer than index finger**
		
☐	☐	☐

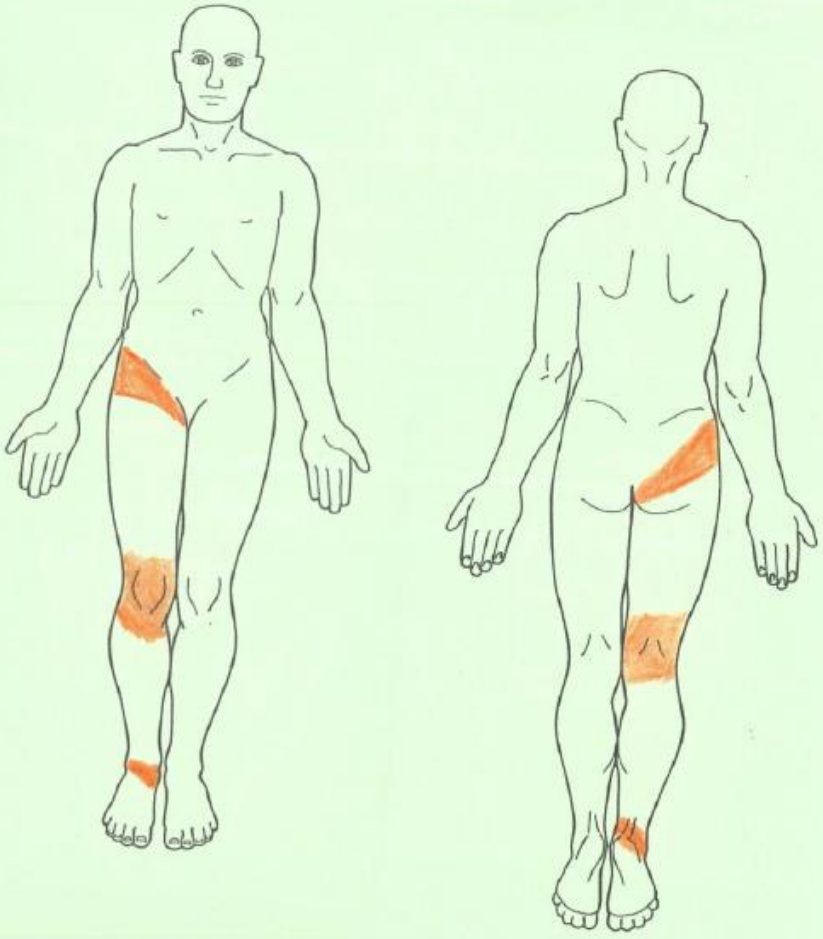
33. Which **hand do you use more often** for writing and brushing your teeth?

☐ Right-Handed ☐ Left-Handed ☐ Equally Proficient

12

SECTION 6: About Pain Anywhere in your Body

34. This question is about **recent pain** you may have 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 previous month**. By pain we also mean aching, discomfort and/or stiffness. Please **do not include** pain due to feverish illness such as the flu. If you **do not have any body pain** that has lasted one day or longer in the last 4 weeks, please tick this box ☐ and move to **SECTION 7**.



35. How much physical pain have you had during the **past 4 weeks**? *(please tick one)*

None	Very mild	Mild	Moderate	Severe	Very Severe
☐	☐	☐	☐	☐	☐

36. If you answered "moderate" or "severe" or "very severe", has this pain lasted **more than 3 months?**

☐ Yes ☐ No

37. Of the areas highlighted on the previous page, where do you have the strongest pain or the one that disturbs you the most?

_____

in the past 12 mo

38. Have you ~~ever~~ consulted a doctor (GP or hospital) about this pain in your body?

☐ Yes ☐ No

14

HADS

SECTION 7: The Way You Feel

39. The following questions are designed to help us to know how you feel. Read each item below and place tick ✓ the box next to the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies. Your immediate reaction to each item will probably be more accurate than a long, thought-out response.

a. I feel tense or 'wound up'
- ☐ most of the time
- ☐ a lot of the time
- ☐ from time to time, occasionally
- ☐ not at all

b. I still enjoy the things I used to enjoy
- ☐ definitely as much
- ☐ not quite so much
- ☐ only a little
- ☐ hardly at all

c. I get a sort of frightened feeling as if something awful is about to happen
- ☐ very definitely and quite badly
- ☐ yes, but not too badly
- ☐ a little, but it doesn't worry me
- ☐ not at all

d. I can laugh and see the funny side of things
- ☐ as much as I always could
- ☐ not quite so much now
- ☐ definitely not so much now
- ☐ not at all

e. Worrying thoughts go through my mind
- ☐ a great deal of the time
- ☐ a lot of the time
- ☐ not too often
- ☐ very little

f. I feel cheerful
- ☐ never
- ☐ not often
- ☐ sometimes
- ☐ most of the time

g. I can sit at ease and feel relaxed
- ☐ definitely
- ☐ usually
- ☐ not often
- ☐ not at all

h. I feel as if I am slowed down
- ☐ nearly all the time
- ☐ very often
- ☐ sometimes
- ☐ not at all

i. I get a sort of frightened feeling like 'butterflies' in the stomach
- ☐ not at all
- ☐ occasionally
- ☐ quite often
- ☐ very often

j. I have lost interest in my appearance
- ☐ definitely
- ☐ I don't take as much care as I should
- ☐ I may not take quite as much care
- ☐ I take just as much care as ever

k. I feel restless as if I have to be on the move
- ☐ very much indeed
- ☐ quite a lot
- ☐ not very much
- ☐ not at all

l. I look forward with enjoyment to things
- ☐ as much as I ever did
- ☐ rather less than I used to
- ☐ definitely less than I used to
- ☐ hardly at all

m. I get sudden feelings of panic
- ☐ very often indeed
- ☐ quite often
- ☐ not very often
- ☐ not at all

n. I can enjoy a good book or radio or television programme
- ☐ often
- ☐ sometimes
- ☐ not often
- ☐ very seldom

15

SECTION 8: About your Quality of Life

We want to know how you react to illness or pain. Please answer all questions below. Tick one answer even if you cannot answer accurately. Answer the other few questions with a few words or sentences.

40. How often do you see a doctor? in the past year.

☐ Almost never ☐ Only very rarely ☐ About 4 times a year ☐ About once a month ☐ About once a week

41. How many different doctors, chiropractors or other health specialists have you seen in the past year?

☐ None ☐ 1 ☐ 2 or 3 ☐ 4 or 5 ☐ 6 or more

42. How many times have you had treatment during the past year? (For example, drugs, change of drugs, surgery, etc.)

☐ None ☐ 1 ☐ 2 or 3 ☐ 4 or 5 ☐ 6 or more

If yes, what were the treatments?

_____

_____

The next three questions concern your bodily symptoms (for example, pain, aches, pressure in your body, breathing difficulties, tiredness, etc.).

SF12 43. Does your pain or other bodily symptoms stop you from working (including both work outside the home and your housework)?

☐ No ☐ Rarely ☐ Sometimes ☐ Often ☐ Most of the time

44. Does your pain or other bodily symptoms stop you from concentrating on what you are doing?

☐ No ☐ Rarely ☐ Sometimes ☐ Often ☐ Most of the time

45. Does your pain or other bodily symptoms stop you from enjoying yourself?

☐ No ☐ Rarely ☐ Sometimes ☐ Often ☐ Most of the time

16

46. In general, would you say your health currently is:

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

47. The following questions are about activities you may do during a typical day. **Would your health limit you** in these activities? If so, how much?

	Yes, Limited a lot	Yes, Limited a little	Not, limited at all
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
Climbing **several** flights of stairs	☐	☐	☐

48. During the **past month,** have you had any of the following problems with work or other regular daily activities **as a result of your physical health?**

	Yes	No
Accomplished less than you would like	☐	☐
Were **limited** in the **kind** of work or other activities	☐	☐

49. During the **past month,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (e.g. feeling depressed or anxious)?

	Yes	No
Accomplished less than you would like	☐	☐
Didn't do work or other activities as **carefully** as usual	☐	☐

50. During the **past month** how much did **pain** interfere with your normal work (including both work outside the home and housework)?

Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely ☐

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51. These next questions are about how you feel and how things have been with you **during the past month.** Please give the **one** answer that is closest to the way you have been feeling for **each** item.

How much time **during the last month...**

	None of the time	**A little of the time**	**Some of the time**	**A good bit of the time**	**Most of the time**	**All of the time**
Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐

52. During the **past month,** how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting friends, relatives etc).

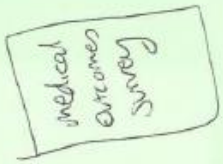
None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
☐	☐	☐	☐	☐	☐

SF12

53. Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, knee pain, hip pain, back pain or muscle pain. We are interested in the types of thoughts and feeling that you have **when you are in pain**. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. **Using the scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.**

	Not At All	Slight Degree	Moderate Degree	Great Degree	All the time
a. I worry all the time about whether the pain will end	☐	☐	☐	☐	☐
b. I feel I can't go on	☐	☐	☐	☐	☐
c. It's terrible and I think it's never going to get any better	☐	☐	☐	☐	☐
d. It's awful and I feel that it overwhelms me	☐	☐	☐	☐	☐
e. I feel I can't stand it anymore	☐	☐	☐	☐	☐
f. I become afraid that the pain will get worse	☐	☐	☐	☐	☐
g. I keep thinking of other painful events	☐	☐	☐	☐	☐
h. I anxiously want the pain to go away	☐	☐	☐	☐	☐
i. I can't seem to keep it out of my mind	☐	☐	☐	☐	☐
j. I keep thinking about how much it hurts	☐	☐	☐	☐	☐
k. I keep thinking about how badly I want the pain to stop	☐	☐	☐	☐	☐
l. There's nothing I can do to reduce the intensity of the pain	☐	☐	☐	☐	☐
m. I wonder whether something serious may happen	☐	☐	☐	☐	☐

PCS



54. How often during the **past 4 weeks** did you:

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. get enough sleep to feel rested in the morning?	☐	☐	☐	☐	☐	☐
b. awaken short of breath or with a headache?	☐	☐	☐	☐	☐	☐
c. have trouble falling asleep?	☐	☐	☐	☐	☐	☐
d. have trouble staying awake during the day	☐	☐	☐	☐	☐	☐

55. **In the past month**, did you feel tired on most days?

☐ Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Always

fatigue / sleep

Thank you very much for taking the time to complete this questionnaire. We would like to emphasise that your contact details and responses will be kept **completely confidential**

We would be grateful if you could now answer the following questions regarding your willingness to participate further in our research.

1] **To enable us to evaluate the development and progression of knee pain, we would like to send you a follow-up questionnaire in approximately one years' time. We would therefore be grateful if you could confirm below whether you are happy to receive a follow up questionnaire and also whether you give your permission for us to contact your GP, the Health and Social Care Information service or other central UK NHS body to confirm your contact details, at the time of mailing the follow up questionnaire:**

No, I do not want to receive a follow up questionnaire ☐

Yes, I would be willing to receive a follow up questionnaire and give my permission for the research team to contact my GP, the Health Social Care Information Service or other central UK NHS body to confirm my contact details ☐

If you have answered '*Yes*' above, please sign and date:

Signature _____ Date _____

2] **Depending on your responses in this questionnaire, you may be eligible to participate in a more detailed assessment which involves a clinical assessment and knee x-rays at Nottingham City Hospital. If you are eligible, would you be interested in receiving information that explains this part of the study in detail? Receiving information would not commit you to being in this study.**

Yes, I would like to receive written information ☐

No, I would not like to receive written information ☐

3] **Finally, your responses to this questionnaire may make you eligible to participate in future research studies on osteoarthritis at the University of Nottingham. If you are interested, please could you indicate this by ticking the relevant box below? Again, receiving further information would not commit you to being in further studies.**

Yes, I would like to receive written information ☐

No, I would not like to receive written information ☐

21

If you have answered yes to the questions on page 21, please confirm your contact details below:

Full Name: _____

Address: _____

_____

_____

Best Daytime Phone Number: _____

If you are happy for us to email you, please provide your email address below:

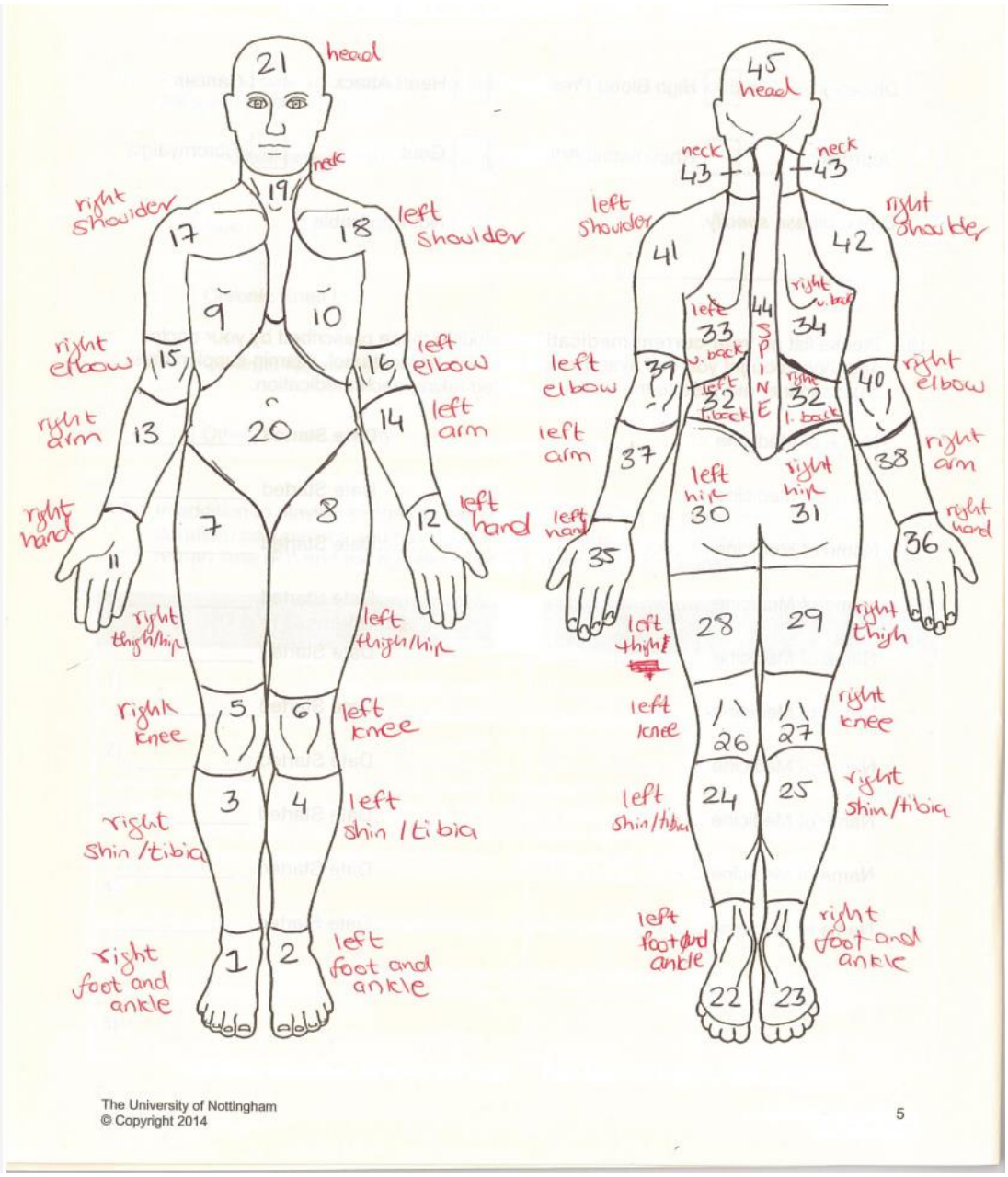
Email address: _____ @ _____

Thank you for your time.

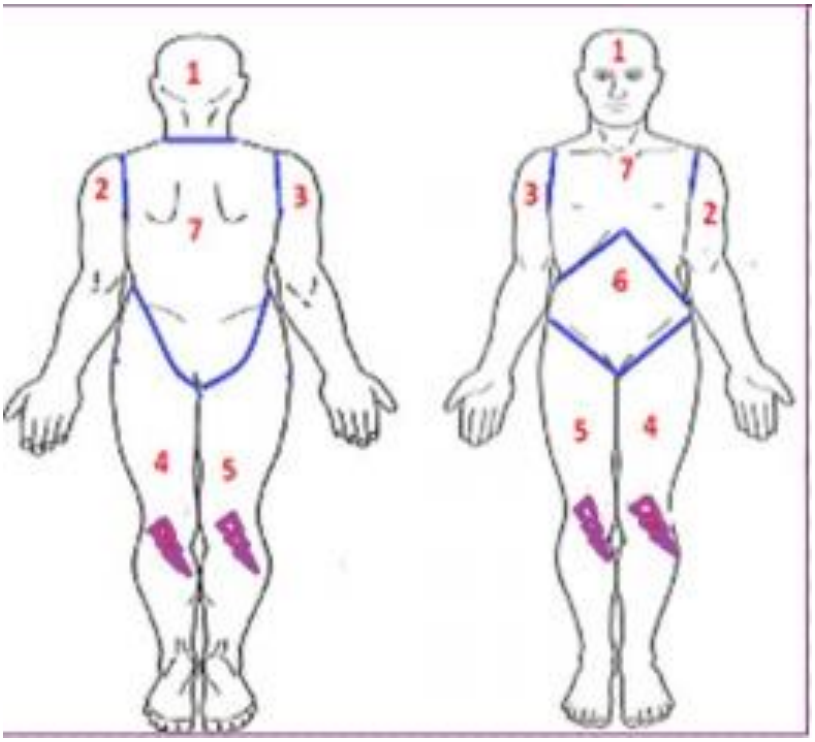
Please return this questionnaire in the pre-paid envelope provided.

Appendix 2. Figure showing Diagrammatic manikin scoring grids.

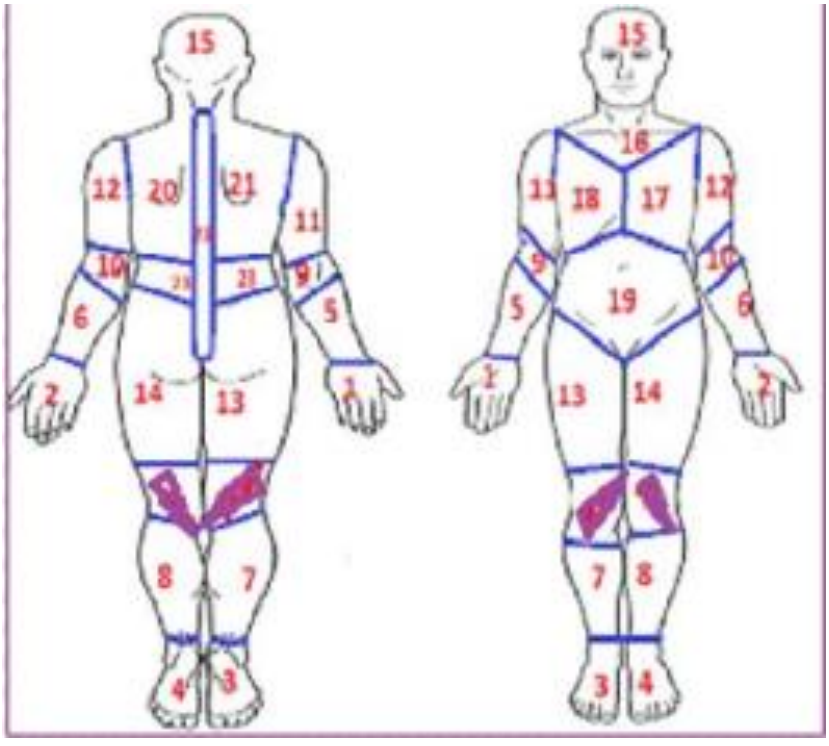
Appendix 2.1. KPIC 45 grid scoring method for the body pain manikin.



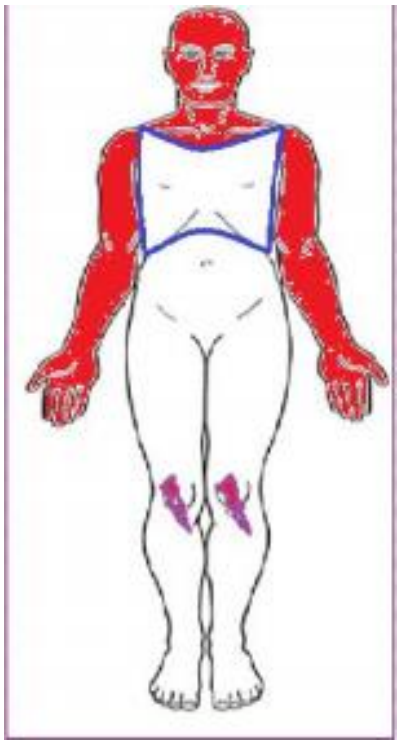
Appendix 2.2. Manikin-scoring grid based on 7 anatomical sites.



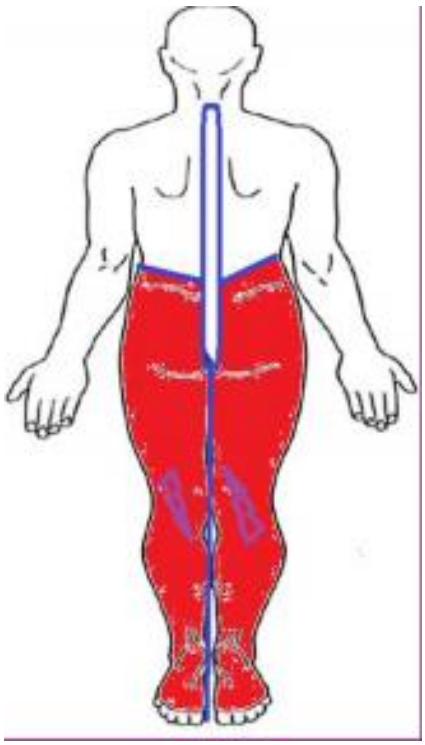
Appendix 2.3. Manikin-scoring grid based on 23 anatomical sites.



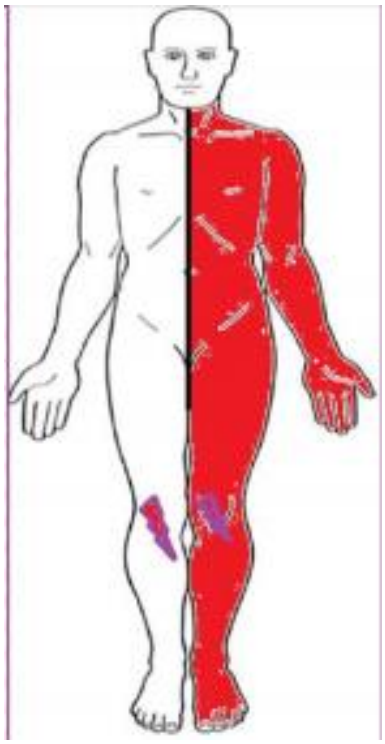
Appendix 2.4. Manikin-scoring grid based on knee pain plus other painful site above waist.



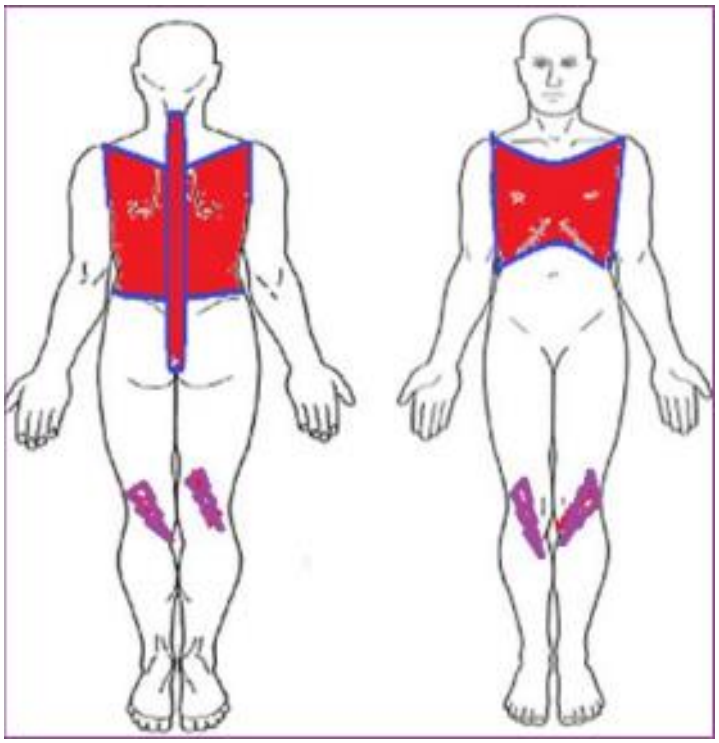
Appendix 2.5. Manikin-scoring grid based on knee pain plus other painful site below waist.



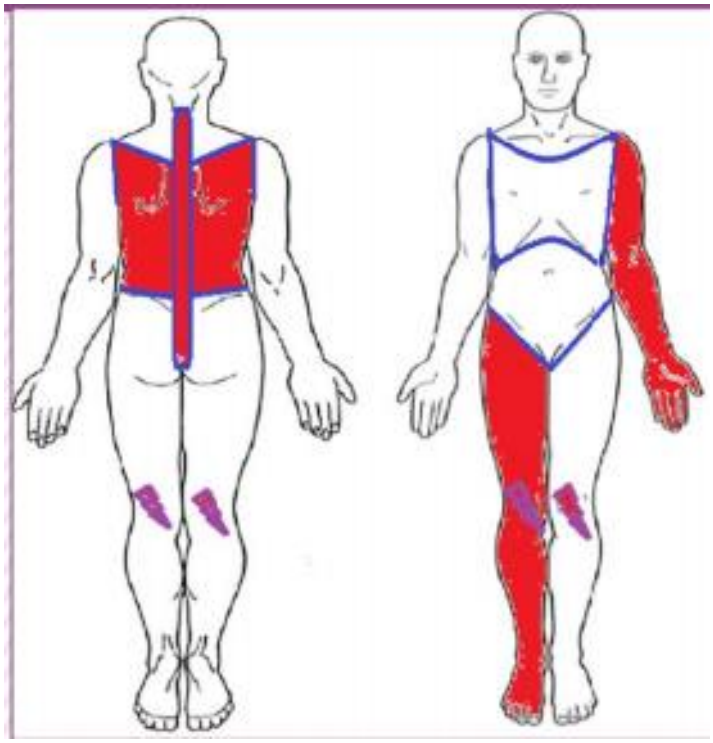
Appendix 2.6. Manikin-scoring grid based on knee pain plus pain in contralateral side.



Appendix 2.7. Manikin-scoring grid based on knee pain plus axial pain.



Appendix 2.8. Manikin-scoring grid based on knee pain plus ACR's widespread pain criteria.



Appendix 3. KPIC 1 Year Follow-up survey.

Nottingham University Hospitals NHS Trust

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Knee Pain and Related Health
Year 1 Follow Up Questionnaire

Knee pain, often due to osteoarthritis, is a very common problem affecting 1 in 4 people over the age of 40. We want to understand why some people are more affected than others and the risk factors and health problems associated with knee pain. You have very kindly already completed a similar questionnaire one year ago and we would like to know whether there have been any changes to your knee pain and related health in the past 12 months.

We would therefore be very grateful if you would take the time to complete this questionnaire, **regardless of whether or not you have knee pain**. We hope you find it interesting. It takes approximately 30-40 minutes to complete. Most of the questions just require a tick in a box, but for others, clear instructions are given.

We would also be grateful if you could confirm, on the last page of the questionnaire, whether you would be willing to complete a follow-up questionnaire in approximately two years' time and, if you are eligible, whether you would like to receive information about further research which will involve a single visit to Nottingham City Hospital, for a clinical assessment and an x-ray.

Please return this questionnaire, in the pre-paid envelope **(no stamp required)** to Academic Rheumatology at the Nottingham City Hospital as soon as possible.

Your answers are strictly confidential

If you have any questions or require any assistance completing the questionnaire please telephone: Nadia Frowd or Laura Marshall on 0115-8231676

Thank you for your assistance with this important area of research.

Chief Investigator – Professor Michael Doherty

Approved by: Nottingham 2 Research Ethics Committee

Funded by: Arthritis Research UK
Providing answers today and tomorrow

Office use only KPIC ID | | | | | |

Version 3, Date 07.07.2015

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SECTION 1: About Yourself

1. What is your Date of Birth?

   ☐☐ Day ☐☐ Month ☐☐☐☐ Year

2. What Sex are you?

   ☐ Male ☐ Female

SECTION 2: About Your Medical History and Medication

3. Have you been diagnosed by your doctor as having osteoarthritis of the knee in the past 12 months?

   ☐ Yes ☐ No

4. Have you been diagnosed with any new medical conditions in the past 12 months?

   _____

5. Have you broken either of your legs in the past 12 months?

   ☐ Yes ☐ No

   If yes, which bone did you break? _____

6. Have you suffered significant injury to either of your knees in the past 12 months that led you to see your doctor?

   ☐ Yes, *please specify*: _____ ☐ No

7. Please list **all** your **current medication** including those **prescribed by your doctor** and those you **bought yourself** over the counter (*please **include any hormonal medication** such as oestrogen supplements, **vitamin supplements and alternative medicines**).*

Name of Medication
1)
2)
3)
4)
5)
6)
7)
8)
9)
10)
11)
12)

SECTION 3: About Your Knee Pain

8. In the past 12 months, have you had any pain in or around a knee on most days for **at least a month**?

☐ Yes ☐ No ***(if No, please go to Section 4)***

9. During the past 12 months, has your knee pain lasted **more than 3 months**?

☐ Yes ☐ No

10. Have you had knee pain on most days of **this past month**?

☐ Yes ☐ No

11. Since it has started, do you think the severity of your knee pain has overall…

☐ Greatly Improved ☐ Slightly Improved ☐ Remained the Same ☐ Worsened

12. Which knee(s) do you / did you experience the pain in?

☐ Right ☐ Left ☐ Both

If both, which overall is the worst knee?

☐ Right ☐ Left ☐ Equal

13. Have you ever had any injections into your knee in the past 12 months?

☐ Yes ☐ No

14. If you answered "**yes**", was it:

☐ Steroid Injection ☐ Hyaluronic Acid Injection ☐ Don't Know

15. Have you had any operation on either of your knees **in the past 12 months**?

☐ Yes ☐ No

If yes, what type of operation did you undergo? *(If you did not undergo one of the specific operations then please leave the related boxes blank)*

Type of Operation	Which Knee? (Right, Left, Both?)	Age at Time of Operation *(years)*
Arthroscopy / Telescope / Keyhole		
Ligament Repair		
Meniscus or Cartilage Removal		
Joint Replacement		
Other, *please specify* _____		

16. In the past 12 months, have you consulted a healthcare professional (eg your GP, a hospital specialist, a physiotherapist etc) about your knee pain?

☐ Yes ☐ No

17. In the past 12 months, approximately how many different things have you tried for your knee pain (including things like drugs, exercise, changes to diet, footwear modifications etc)? Please include <u>everything</u> you have tried, regardless of whether or not it was recommended by a healthcare professional.

☐

18. Which of the various things you have tried has helped your knee pain the most?

_____

19. **The following questions are to be answered by people who have knee pain.**

We want you to tell us about the knee **where you have the greatest pain**. To get a better sense of the different types of knee pain you may experience, we would like to ask you about any "constant pain" (pain you have all the time) separately from any pain that you may experience less often, that is "intermittent" (pain that comes and goes).

We appreciate that some of these questions may seem a bit repetitive but they have been shown to provide important information about knee pain. **Please answer ALL the questions.**

For each of the following questions please select the answer that best describes **on average your constant knee pain in the PAST WEEK.**

	Not at all	Mildly	Moderately	Severely	Extremely
a. In the past week, how intense has your CONSTANT KNEE PAIN been?	☐	☐	☐	☐	☐
b. In the past week, how much has your CONSTANT KNEE PAIN affected your sleep?	☐	☐	☐	☐	☐
c. In the past week, how much has your CONSTANT KNEE PAIN affected your overall quality of life?	☐	☐	☐	☐	☐
d. In the past week, how frustrated or annoyed have you been by your CONSTANT KNEE PAIN?	☐	☐	☐	☐	☐
e. In the past week, how upset or worried have you been by your CONSTANT KNEE PAIN?	☐	☐	☐	☐	☐

20. Now please select the response that best describes **on average your knee pain that comes and goes in the PAST WEEK**

	Not at all	Mildly	Moderately	Severely	Extremely
a. In the past week, how intense has your **knee pain that comes and goes** been?	☐	☐	☐	☐	☐
b. In the past week, how much has your **knee pain that comes and goes** affected your sleep?	☐	☐	☐	☐	☐
c. In the past week, how much has your **knee pain that comes and goes** affected your overall quality of life?	☐	☐	☐	☐	☐
d. In the past week, how frustrated or annoyed have you been by your **knee pain that comes and goes?**	☐	☐	☐	☐	☐
e. In the past week, how upset or worried have you been by your **knee pain that comes and goes?**	☐	☐	☐	☐	☐
f. In the past week, how frequently has this **knee pain that comes and goes** occurred?	☐	☐	☐	☐	☐

We now want to ask you about **any kind of knee pain** that you may be currently experiencing

21. **Over the past month**, in your most painful knee, does pain **run up or down** your leg?

☐ Yes ☐ No

Please tell us about the **intensity of discomfort** you experience in or around your **most painful knee.**

22. How would you rate your most painful knee pain on a 0-10 scale at the present time, that is **right now**, where 0 is 'no pain' and 10 is 'pain as bad as could be'? (Please circle only ONE number)

No Pain										**Pain as bad as it could be**
0	1	2	3	4	5	6	7	8	9	10

23. In the **past month**, how intense was your **'worst knee pain'** rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'? (Circle only ONE number)

No Pain										**Pain as bad as it could be**
0	1	2	3	4	5	6	7	8	9	10

24. In the **past month**, on **average**, how **intense** was the pain in your **most painful knee** rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'? (That is, your usual pain at times you were experiencing pain.) (Circle only ONE number)

No Pain										**Pain as bad as it could be**
0	1	2	3	4	5	6	7	8	9	10

25. This next question is on the pattern of your pain in your **most painful knee.** Which of the 4 different options below is the one that best describes the pattern of your worst knee pain over the past month? (Tick one box)

☐  Persistent pain with slight fluctuations

☐  Persistent pain with pain attacks

☐  Pain attacks without pain between them

☐  Pain attacks with pain between them

26. Please select the response that best describes the **type of pain in your most painful** knee over the **past month**. Please do not leave any questions blank and tick one box.

	Never	Hardly Noticed	Slightly	Moderate	Strongly	Very Strongly
a. Do you suffer from a burning sensation (eg stinging nettles) in or around your most painful knee?	☐	☐	☐	☐	☐	☐
b. Do you have a tingling or prickling sensation in the area of your most painful knee 'pain' (eg like crawling ants or electrical tingling?)	☐	☐	☐	☐	☐	☐
c. Is light touching (clothing, a blanket) in this area painful?	☐	☐	☐	☐	☐	☐
d. Do you have sudden pain attacks in the area of your most painful knee 'pain', like electrical shocks?	☐	☐	☐	☐	☐	☐
e. Is cold or heat (bath water) in this area occasionally painful?	☐	☐	☐	☐	☐	☐
f. Do you suffer from a sensation of numbness in or around your most painful knee?	☐	☐	☐	☐	☐	☐
g. Does slight pressure in this area, (e.g. with a finger), trigger pain?	☐	☐	☐	☐	☐	☐

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27. We would now like to ask you about your knee pain and specifically, how you feel about it. Please circle the number that best corresponds to your views.

a) How much does your knee pain affect your life?

No affect at all										**Severely affects my life**
0	1	2	3	4	5	6	7	8	9	10

b) How long do you think your knee pain will continue?

A very short time										**Forever**
0	1	2	3	4	5	6	7	8	9	10

c) How much control do you feel you have over your knee pain?

Absolutely no control										**Extreme amount of control**
0	1	2	3	4	5	6	7	8	9	10

d) How much do you think your treatment can help your knee pain?

Not at all										**Extremely helpful**
0	1	2	3	4	5	6	7	8	9	10

e) How concerned are you about your knee pain?

Not at all concerned										**Extremely concerned**
0	1	2	3	4	5	6	7	8	9	10

f) How well do you feel you understand your knee pain?

Don't understand at all										**Understand very clearly**
0	1	2	3	4	5	6	7	8	9	10

g) How much does your knee pain affect you emotionally? (e.g. does it make you angry, scared, upset or depressed)?

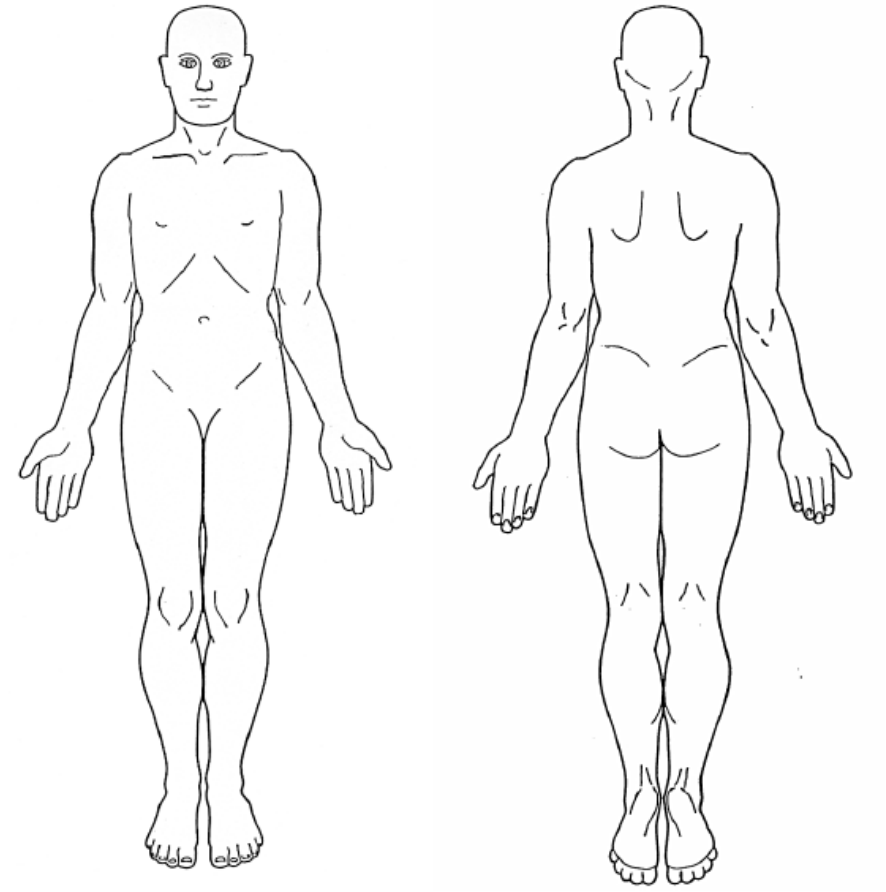
Not at all affected emotionally										**Extremely affected emotionally**
0	1	2	3	4	5	6	7	8	9	10

h) Please list in rank order the three most important factors that you believe caused your knee pain. The most important causes for me are:

1) _____ 2) _____ 3) _____

SECTION 4: About Pain Anywhere in your Body

28. This question is about **recent 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 previous month.** By pain we also mean aching, discomfort and/or stiffness. Please **do not include** pain due to feverish illness such as flu. If you **do not have any body pain** that has lasted one day or longer in the last 4 weeks, please tick this box ☐ and move to question 33.



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29. How much physical pain have you had during the **past 4 weeks**? *(please tick one)*

None	Very mild	Mild	Moderate	Severe	Very Severe
☐	☐	☐	☐	☐	☐

30. If you answered "moderate" or "severe" or "very severe", has this pain lasted **more than 3 months?**

☐ Yes ☐ No

31. Of the areas highlighted on the previous page, where do you have the strongest pain or the one that disturbs you the most?

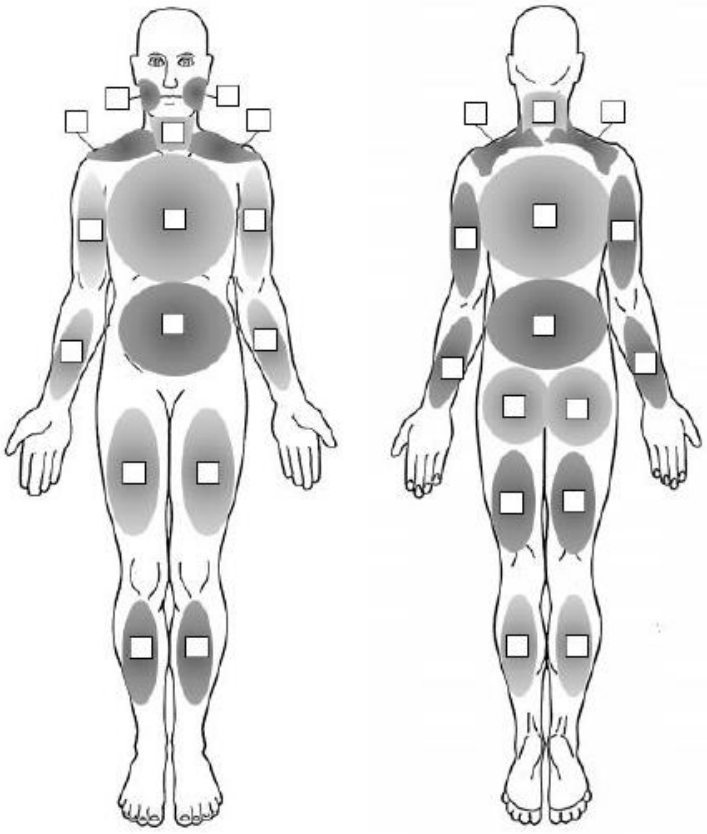
_____

32. In the past 12 months, have you consulted a doctor (GP or hospital) about this pain in your body?

☐ Yes ☐ No

33. We are still interested in your body pain experience particularly in the past one week. Please can you think of your pain and symptoms but exclude any that have been due to known illnesses such as arthritis, lupus etc.

In the diagrams below, please tick the boxes ☐ where you have experienced pain in the region indicated by the shaded areas. Please tick all relevant boxes (the boxes are either placed in the area itself or joined to the area by a line).



34. Please could you indicate in the tick boxes your level of symptom severity score over the past week using the following scale.

	0 = No problem	1 = Slight or mild problems; generally mild or intermittent	2= Moderate; considerable problems; often present and/or at a moderate level	3= Severe: pervasive, continuous, life disturbing problems
a) Tiredness	☐	☐	☐	☐
b) Waking Unrefreshed	☐	☐	☐	☐
c) Concentration (Forgetfulness and problem solving)	☐	☐	☐	☐

35. Lastly, which of the following symptoms have you experienced in the past 1 week? Please tick all that apply

- ☐ Muscle pain
- ☐ Muscle Weakness
- ☐ Numbness/tingling
- ☐ Fever
- ☐ Irritable bowel syndrome
- ☐ Pain/cramps in abdomen
- ☐ Constipation
- ☐ Pain in upper abdomen
- ☐ Nausea
- ☐ Diarrhoea
- ☐ Dry Mouth
- ☐ Vomiting
- ☐ Heartburn
- ☐ Oral ulcers
- ☐ Loss/change in taste
- ☐ Loss of appetite
- ☐ Fatigue/Tiredness
- ☐ Thinking/ problems remembering
- ☐ Headache
- ☐ Dizziness
- ☐ Depression
- ☐ Nervousness
- ☐ Blurred vision
- ☐ Fits
- ☐ Chest Pain
- ☐ Wheezing
- ☐ Shortness of breath
- ☐ Ringing in ears
- ☐ Dry Eyes
- ☐ Hearing difficulties
- ☐ Itching
- ☐ Raynaud's*
- ☐ Hives**
- ☐ Rash
- ☐ Sun sensitivity
- ☐ Easy bruising
- ☐ Hair loss
- ☐ Frequent urination
- ☐ Painful urination
- ☐ Bladder pain

**Raynaud's: Sudden painful whitening of several fingers with numbness and tingling*
***Hives: normally raised itchy small pale skin swellings which come and go quickly*

SECTION 5: The Way You Feel

36. The following questions are designed to help us to know how you feel. Please read each item below and tick (✓) the box next to the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies. Your immediate reaction to each item will probably be more accurate than a long, thought-out response.

a. I feel tense or 'wound up'
☐ most of the time
☐ a lot of the time
☐ from time to time, occasionally
☐ not at all

b. I still enjoy the things I used to enjoy
☐ definitely as much
☐ not quite so much
☐ only a little
☐ hardly at all

c. I get a sort of frightened feeling as if something awful is about to happen
☐ very definitely and quite badly
☐ yes, but not too badly
☐ a little, but it doesn't worry me
☐ not at all

d. I can laugh and see the funny side of things
☐ as much as I always could
☐ not quite so much now
☐ definitely not so much now
☐ not at all

e. Worrying thoughts go through my mind
☐ a great deal of the time
☐ a lot of the time
☐ not too often
☐ very little

f. I feel cheerful
☐ never
☐ not often
☐ sometimes
☐ most of the time

g. I can sit at ease and feel relaxed
☐ definitely
☐ usually
☐ not often
☐ not at all

h. I feel as if I am slowed down
☐ nearly all the time
☐ very often
☐ sometimes
☐ not at all

i. I get a sort of frightened feeling like 'butterflies' in the stomach
☐ not at all
☐ occasionally
☐ quite often
☐ very often

j. I have lost interest in my appearance
☐ definitely
☐ I don't take as much care as I should
☐ I may not take quite as much care
☐ I take just as much care as ever

k. I feel restless as if I have to be on the move
☐ very much indeed
☐ quite a lot
☐ not very much
☐ not at all

l. I look forward with enjoyment to things
☐ as much as I ever did
☐ rather less than I used to
☐ definitely less than I used to
☐ hardly at all

m. I get sudden feelings of panic
☐ very often indeed
☐ quite often
☐ not very often
☐ not at all

n. I can enjoy a good book or radio or television programme
☐ often
☐ sometimes
☐ not often
☐ very seldom

37. The following questions are about your feelings in general. Please answer the following questions about yourself by indicating the extent of your agreement with the scale. Be as honest as you can and try not to let your responses to one question influence your response to other questions. There are no right or wrong answers.

	Disagree Strongly	Disagree	Neither agree nor disagree	Agree	Strongly Agree
a. In uncertain times, I usually expect the best.	☐	☐	☐	☐	☐
b. It's easy for me to relax	☐	☐	☐	☐	☐
c. If something can go wrong for me, it will	☐	☐	☐	☐	☐
d. I'm always optimistic about my future.	☐	☐	☐	☐	☐
e. I enjoy my friends a lot.	☐	☐	☐	☐	☐
f. It's important for me to keep busy.	☐	☐	☐	☐	☐
g. I hardly ever expect things to go my way.	☐	☐	☐	☐	☐
h. I don't get upset too easily.	☐	☐	☐	☐	☐
i. I rarely count on good things happening to me.	☐	☐	☐	☐	☐
j. Overall, I expect more good things to happen to me than bad.	☐	☐	☐	☐	☐

38. In the table below please tick a box to explain how well the pairs of words to describe you, even if one characteristic applies more strongly than the other.

	Disagree Strongly	Disagree Moderately	Disagree a little	Neither agree nor disagree	Agree a little	Agree moderately	Agree Strongly
a. Extroverted Enthusiastic	☐	☐	☐	☐	☐	☐	☐
b. Critical Quarrelsome	☐	☐	☐	☐	☐	☐	☐
c. Dependable Self-disciplined	☐	☐	☐	☐	☐	☐	☐
d. Anxious Easily upset	☐	☐	☐	☐	☐	☐	☐
e. Open to new experiences Complex	☐	☐	☐	☐	☐	☐	☐
f. Reserved Quiet	☐	☐	☐	☐	☐	☐	☐
g. Sympathetic Warm	☐	☐	☐	☐	☐	☐	☐
h. Disorganised Careless	☐	☐	☐	☐	☐	☐	☐
i. Calm Emotionally stable	☐	☐	☐	☐	☐	☐	☐
j. Conventional Uncreative	☐	☐	☐	☐	☐	☐	☐

SECTION 6: About Your Sleep Quality

Sleep and waking up refreshed is an important part of a healthy lifestyle. We would like to ask you a few questions on your sleeping patterns during the past 4 weeks.

39. During the past 4 weeks, how long did it usually take you to fall asleep? *Please tick the appropriate box.*

Over 60 minutes	0-15 minutes	16-30 minutes	31-45 minutes	45-60 minutes
☐	☐	☐	☐	☐

40. During the past 4 weeks, how many hours did you sleep each night?

Number of hours per night _____

41. How often in the past 4 weeks did you... *(Please tick the most appropriate box in each line)*

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Feel that your sleep was not quiet (*moving restlessly, feeling tense, speaking, etc., while sleeping*)?	☐	☐	☐	☐	☐	☐
b. Get enough sleep to feel rested upon waking in the morning?	☐	☐	☐	☐	☐	☐
c. Awaken short of breath or with a headache?	☐	☐	☐	☐	☐	☐
d. Feel drowsy or sleepy during the day?	☐	☐	☐	☐	☐	☐
e. Have trouble falling asleep?	☐	☐	☐	☐	☐	☐
f. Awaken during your sleep time and have trouble falling asleep again?	☐	☐	☐	☐	☐	☐
g. Have trouble staying awake during the day?	☐	☐	☐	☐	☐	☐
h. Snore during your sleep?	☐	☐	☐	☐	☐	☐
i. Taking naps (5 minutes or longer) during the day?	☐	☐	☐	☐	☐	☐
j. Get the amount of sleep you need?	☐	☐	☐	☐	☐	☐

SECTION 7: About Your Quality of Life

We want to know how you react to illness or pain. Please answer all questions below. Tick one answer even if you cannot answer accurately. Answer the other few questions with a few words or sentences.

42. How often did you see your doctor in the past 12 months?

☐ Almost never ☐ Only very rarely ☐ About 4 times a year ☐ Over 4 times a year

43. How many different doctors, chiropractors or other health specialists have you seen in the past 12 months?

☐ None ☐ 1 ☐ 2 or 3 ☐ 4 or 5 ☐ 6 or more

44. How many times have you had treatment during the past 12 months? (For example, drugs, change of drugs, surgery, etc.)

☐ None ☐ 1 ☐ 2 or 3 ☐ 4 or 5 ☐ 6 or more

If yes, what were the treatments?

_____

_____

The next three questions concern your bodily symptoms (for example, pain, aches, pressure in your body, breathing difficulties, tiredness, etc.).

45. Does your pain or other bodily symptoms stop you from working (including both work outside the home and your housework)?

☐ No ☐ Rarely ☐ Sometimes ☐ Often ☐ Most of the time

46. Does your pain or other bodily symptoms stop you from concentrating on what you are doing?

☐ No ☐ Rarely ☐ Sometimes ☐ Often ☐ Most of the time

47. Does your pain or other bodily symptoms stop you from enjoying yourself?

☐ No ☐ Rarely ☐ Sometimes ☐ Often ☐ Most of the time

48. In general, would you say your health currently is:

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

49. The following questions are about activities you may do during a typical day. **Would your health limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	Not, limited at all
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
Climbing **several** flights of stairs	☐	☐	☐

50. During the **past month,** have you had any of the following problems with work or other regular daily activities **as a result of your physical health?**

	Yes	No
Accomplished less than you would like	☐	☐
Were **limited** in the **kind** of work or other activities	☐	☐

51. During the **past month,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (e.g. feeling depressed or anxious)?

	Yes	No
Accomplished less than you would like	☐	☐
Didn't do work or other activities as **carefully** as usual	☐	☐

52. During the **past month** how much did **pain** interfere with your normal work (including both work outside the home and housework)?

Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely ☐

53. These next questions are about how you feel and how things have been with you **during the past month.** Please give the **one** answer that is closest to the way you have been feeling for **each** item.

How much time **during the last month…**

	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐

54. During the **past month**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting friends, relatives etc).

None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
☐	☐	☐	☐	☐	☐

55. Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, knee pain, hip pain, back pain or muscle pain. We are interested in the types of thoughts and feeling that you have **when you are in pain**. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. **Using the scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.**

	Not At All	Slight Degree	Moderate Degree	Great Degree	All the time
a. I worry all the time about whether the pain will end	☐	☐	☐	☐	☐
b. I feel I can't go on	☐	☐	☐	☐	☐
c. It's terrible and I think it's never going to get any better	☐	☐	☐	☐	☐
d. It's awful and I feel that it overwhelms me	☐	☐	☐	☐	☐
e. I feel I can't stand it anymore	☐	☐	☐	☐	☐
f. I become afraid that the pain will get worse	☐	☐	☐	☐	☐
g. I keep thinking of other painful events	☐	☐	☐	☐	☐
h. I anxiously want the pain to go away	☐	☐	☐	☐	☐
i. I can't seem to keep it out of my mind	☐	☐	☐	☐	☐
j. I keep thinking about how much it hurts	☐	☐	☐	☐	☐
k. I keep thinking about how badly I want the pain to stop	☐	☐	☐	☐	☐
l. There's nothing I can do to reduce the intensity of the pain	☐	☐	☐	☐	☐
m. I wonder whether something serious may happen	☐	☐	☐	☐	☐

56. **In the past month**, did you feel tired on most days?

☐ Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Always

Thank you very much for taking the time to complete this questionnaire.
We would like to emphasise that your contact details and responses will be kept **completely confidential**

We would be grateful if you could now answer the following questions regarding your willingness to participate further in our research.

1] **To enable us to evaluate the development and progression of knee pain, we would like to send you a follow-up questionnaire in approximately two years' time. We would therefore be grateful if you could confirm below whether you are happy to receive a follow up questionnaire and also whether you give your permission for us to contact your GP, the Health and Social Care Information Service or other central UK NHS body to confirm your contact details, at the time of mailing the follow up questionnaire:**

No, I do not want to receive a follow up questionnaire ☐

Yes, I would be willing to receive a follow up questionnaire and give my permission for the research team to contact my GP, the Health Social Care Information Service or other central UK NHS body to confirm my contact details ☐

If you have answered '*Yes*' above, please sign and date:

_____ _____
Signature Date

2] **Depending on your responses in this questionnaire, you may be eligible to participate in a more detailed assessment which involves a clinical assessment and knee x-rays at Nottingham City Hospital. If you are eligible, would you be interested in receiving information that explains this part of the study in detail? Receiving information would not commit you to being in this study.**

Yes, I would like to receive written information ☐

No, I would not like to receive written information ☐

3] **Finally, your responses to this questionnaire may make you eligible to participate in future research studies on osteoarthritis at the University of Nottingham. If you are interested, please could you indicate this by ticking the relevant box below? Again, receiving further information would not commit you to being in further studies.**

Yes, I would like to receive written information ☐

No, I would not like to receive written information ☐

24

If you have answered yes to the questions on page 24, please confirm your contact details below:

Full Name: _____

Address: _____

_____

_____

Best Daytime Phone Number: _____

If you are happy for us to email you, please provide your email address below:

Email address: _____ @ _____

Thank you for your time.

Please return this questionnaire in the pre-paid envelope provided.

Appendix 4. Participant facing documents for the CAP-Knee study.

Appendix 4.1. CAP-Knee study survey.

Arthritis Research UK | pain centre

University of Nottingham UK | CHINA | MALAYSIA

Helping to develop a new questionnaire about knee pain experience

In this part of the study, we want to learn about you, your general health, and how reliable the CAP-Knee scale can be in individuals with knee pain.

We would be very grateful if you would take the time to complete this questionnaire, **regardless of whether or not you have suffered from these problems**.

We would also be grateful if you could indicate, on the last pages of the questionnaire, whether you are willing to receive information about further research that we are doing in the Arthritis Research UK Pain Centre.

Please return this questionnaire, in the addressed pre-paid envelope **(no stamp required)** to us as soon as convenient.

Your answers will be kept strictly confidential

If you have any questions or require any advice on completing the questionnaire please telephone the lead researcher, Kehinde Akin-Akinyosoye on 0115-8231759, kehinde.akin@nottingham.ac.uk.

Chief Investigator: Professor David Walsh

Approved by: Nottingham Research Ethics Committee 1

Funded by: Arthritis Research UK and the University of Nottingham

Person ID: ☐☐☐

Person ID: ☐☐☐

Section A: Information about you and your treatments

What is your **date of birth?**

☐☐ Day ☐☐ Month ☐☐☐☐ Year

What is your **sex?**

☐ Male ☐ Female ☐ Prefer not to say

Choose one option that best describes your **ethnic group** or **background?**

☐ White ☐ Asian ☐ Black

Any other ethnic group (please describe)

What is your **height?**

☐ Feet ☐☐ inches **OR** ☐☐☐ centimetres

How much do you **weigh** with your clothes on but without shoes?

☐☐ stones ☐☐ pounds **OR** ☐☐☐ kilograms

One year ago how much did you **weigh** with your clothes on but without shoes?

☐☐ stones ☐☐ pounds **OR** ☐☐☐ kilograms

What is your **smoking** status?

☐ Smoker ☐ Ex-smoker **OR** ☐ Never smoked

Do you drink usually 3 units or more of **alcohol** per day?

3 units might, for example, be 2 pints of lager, 2 glasses of wine or 3 single shots of spirit.

☐ Yes ☐ No

Person ID

Has a doctor told you that you have any of these medical conditions or problems?
If yes, please place a tick in the boxes provided.

- ☐ Angina
- ☐ Arthritis
- ☐ Asthma
- ☐ Back or spine problems
- ☐ Cancer (not minor skin cancers)
- ☐ Dementia
- ☐ Diabetes mellitus
- ☐ Fibromyalgia
- ☐ Gout
- ☐ Heart attack
- ☐ Heart failure
- ☐ Hypertension
- ☐ Kidney disease
- ☐ Lung disease
- ☐ Osteoarthritis
- ☐ Osteoporosis
- ☐ Rheumatoid arthritis
- ☐ Stroke

Others (please specify any conditions not listed above)

Medicines including pain killers

Please write down the names of any medications, including any pain killers, that you use. They can be prescriptions or bought over the counter.

Names of medications

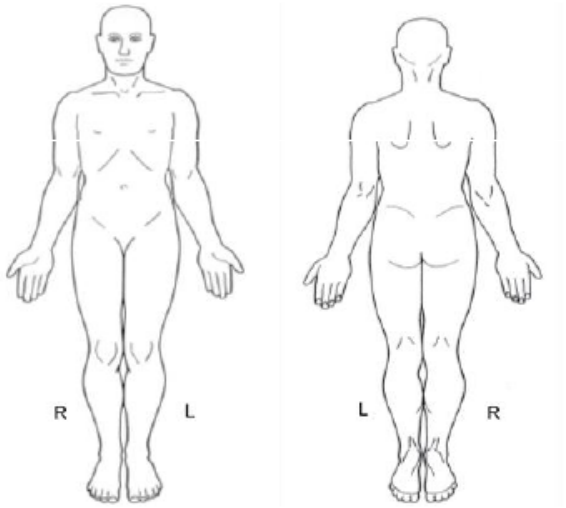
Person ID: ☐☐☐

Section B: CAP-Knee (Central Aspects of Pain in the Knee) Scale

Please select the response that best describes how you have felt over the PAST *WEEK*. Please tick one box only per statement and try not to leave any statements blank.

	Never	Sometimes	Often	Always
1. Cold or heat touching my knee was painful	☐	☐	☐	☐
2. I generally felt tired	☐	☐	☐	☐
3. Knee pain stopped me concentrating on what I was doing	☐	☐	☐	☐
4. I kept thinking about how much my knee hurts	☐	☐	☐	☐
5. In general, I got sudden feelings of panic	☐	☐	☐	☐
6. Knee pain affected my sleep	☐	☐	☐	☐
7. I generally still enjoyed the things I used to enjoy	☐	☐	☐	☐

8. This final 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.



Person ID: ☐☐☐

Section C: Joint Aches and Pains

1. Over the **past 4 weeks**, have you had **pain** or **aching** in **any of your joints**?

☐ Yes ☐ No If you answer 'No', please move to section D.

Most bothersome joint

2. Over the **past 4 weeks**, where was your most bothersome joint pain or aching?

☐ Jaw	☐ Wrist	☐ Neck
☐ Back or spine	☐ Knee	☐ Ankle
☐ Shoulder	☐ Hand or finger	☐ Foot or toe
☐ Elbow	☐ Hip	

3. Over the **past 4 weeks**, how intense was your **average pain** or the **average aching feeling in your most bothersome joint**, where 0 is 'no pain' and 10 is 'pain as bad as could be'?

No pain — Pain as bad as could be

0	1	2	3	4	5	6	7	8	9	10

4. Was your **most bothersome joint** painful for **most days** of the last **4 weeks**?

☐ Yes ☐ No

Section D: Your activities and general health

1. Which is your level of physical activity?

☐ Regular physical activity (at least 2-4 hours per week) ☐ None or mainly sedentary

2. By yourself and not using aids, do you have any difficulty walking up 10 steps without resting?

☐ Yes ☐ No

3. How much of the time during the past 4 weeks did you feel tired?

☐ All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time

4. Do you have any difficulty gripping with your hands (e.g. opening a jam jar)?

☐ Yes ☐ No

5. How much of the time during the past 4 weeks did you feel tired?

☐ All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time

Thank you very much for taking the time to complete this questionnaire.

Person ID:

Thank you very much for taking the time to complete this questionnaire.

Person ID: ☐☐☐

Thank you very much for taking the time to complete this questionnaire.
We would like to emphasise that your contact details and responses will be kept **completely confidential**

Please return this questionnaire in the pre-paid envelope provided.

Researchers at the Arthritis Research UK Pain Centre might wish to contact you with further information.

Receiving further information will not commit you to joining any studies.

Are you willing to be contacted about our research?

Yes, I would like to be contacted ☐

No, I would not like to be contacted ☐

If you have answered 'Yes', please give your contact details below:

Full Name: _____

Address: _____

_____

Postcode: _____

Best Daytime Phone Number: _____

Email address: _____ @ _____

Office use only

Person ID ☐☐☐☐☐ Surgery ID ☐☐☐

Appendix 4.2. CAP-Knee study invitation letter.

¶
XXXXXXXXXXXXXXXXXXXX¶
XXXXXXXXXXXXXXXXXXXX¶
XXXXXXXXX¶
Nottingham¶
NXX-XXX¶
¶
Dear·XXXXXXXXX,¶
¶
The·University·of·Nottingham·wishes·to·invite·you·to·take·part·in·some·research·exploring·how· individuals·interpret·the·questions·included·within·a·newly·developed·questionnaire·-·The·Central· Aspect·of·Pain·in·the·Knee·(CAP-Knee)·Scale.·¶
¶
The·research·would·involve·you·either·taking·part·in·a·short·face-to-face·interview,·and/or·may· involve·you·completing·the·questionnaire·on·two·different·occasions.·You·are·receiving·this·invite· [because·your·clinician·understands·that·you·have·knee·pain]/·[because·you·are·involved·in·the· xxxxxxxxxx·study·and·have·indicated·that·you·are·happy·to·be·contacted·about·future·research· opportunities],·or·have·otherwise·expressed·an·interest·in·participating.¶
¶
Please·find·enclosed·a·Participant·Information·Sheet·with·further·details·of·this·new·research.·If· you·would·like·to·take·part·this·study,·then·please·complete·the·reply·slip·and·return·it·to·the· research·team·in·the·self-addressed·envelope·provided.·If·you·would·like·to·ask·any·questions· about·the·research·before·you·return·the·reply·slip,·then·you·can·contact·the·research·team·on· 0115·823·1759·and·someone·will·be·happy·to·help·with·additional·information.·Once·the·research· team·has·received·your·reply·slip,·you·would·be·contacted·by·them·to·check·whether·they·can· include·you·in·the·study.·¶
¶
If·you·do·not·wish·to·take·part·in·this·research,·then·you·do·not·need·to·take·any·further·action.· Your·participation·in·other·research·studies·and·any·clinical·care·you·might·be·receiving·will·not·be· affected·by·your·decision·whether·or·not·to·take·part·in·this·study.¶
¶
Thank·you·for·considering·participation·in·this·research.¶
¶
Yours·sincerely,¶
¶
[Insert·Clinician·Name·and·details]/·[Insert·ARUK·recruitment·officer·Name·and·details].¶
¶

Appendix 4.3. CAP-Knee study Reply Slip.

Arthritis Research UK | pain centre

University of Nottingham UK | CHINA | MALAYSIA

Helping to develop a new questionnaire about the knee pain experience:

Study Reply Slip

Please contact me about this project ☐

Please do not contact me about this project ☐

Name: _____

Telephone number: _____

Mobile number: _____

Email address: _____

ARUK Pain Centre
Helping to develop a new questionnaire about the knee pain experience
Patient Reply Slip Final Version 1.0: 01_12_17

Appendix 4.4. CAP-Knee Study Participant Information Sheet.

ARUK Pain Centre
A26 Academic Rheumatology
Clinical Sciences Building
City Hospital
Nottingham
NG5 1PB

PARTICIPANT INFORMATION SHEET

(Final Version 1.0: 01_12_17)

IRAS Project ID: 234856

Title of Study: Helping to develop a new questionnaire about the knee pain experience

Name of Researchers: Kehinde Akin-Akinyosoye, Principal Investigator
Professor David Walsh, Professor of Rheumatology
Professor Roshan das Nair, Professor of Clinical Psychology
Professor Eamon Ferguson, Professor of Health Psychology

Introduction

We would like to invite you to take part in our research study. Before you decide, we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is the purpose of this study?

Knee pain can affect anyone, and is a leading cause of disability in later life when it is often due to osteoarthritis. Around half of patients with knee osteoarthritis still report worsening pain despite treatment. The way that a person's brain processes pain signals (central mechanisms) can affect knee pain and whether or not it will get better with treatment.

We are developing a questionnaire, the Central Aspect of Pain in the Knee (CAP-Knee) Scale, to help identify individuals whose knee pain may be being worsened by central mechanisms. Future research with this questionnaire would work out which specific treatments might best help these individuals. Before using the CAP-Knee scale to help make treatment decisions, we need to be confident that it is reliable.

The current study will help us get a better understanding of how individuals with knee pain understand the questions included within the CAP-Knee Scale, and whether different people (for example, men or women) interpret the questions differently. We are also interested in ensuring that the scale is reliable at different time points.

This study is running over at least two months, although your participation in the study would only take up half a day.

Why have I been invited?

We are asking you to participate either because your clinician understands that you have knee pain, or because you indicated through your participation in previous research that you have knee pain and are

happy to be contacted about future research opportunities. We are seeking 30 participants like you to take part in interviews, and 50 people (which may include individuals taking part in the interview study) to complete the CAP-Knee scale on two different occasions.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form before taking part in interviews. If you decide to take part you are still free to withdraw at any time and without giving a reason. This would not affect your legal rights. Participating in this study will not affect your continuing inclusion in other ongoing research studies nor will it affect any clinical care that you receive now or in the future.

What will happen to me if I take part?

If you are interested in participating in this study, a researcher will call you to check that we can include you. If so, you will be offered a convenient date and time to visit the University of Nottingham for a one-off interview, according to your availability. Interviews will be audio-recorded in order to enable us to analyse them. During the interview, you will be shown 8 questions about your pain, mood and other symptoms. You will be asked about what each question means to you, and how you choose an answer. Your knee will be briefly examined by a researcher. You will then be asked to fill in a paper copy questionnaire including the CAP Knee scale and other questions about your knee pain. Your participation in this study would take up to 60 minutes in total.

You will be invited to complete the CAP-Knee scale questionnaire at home one week after your interview, and return it by post in the prepaid envelope provided. Completing this questionnaire will usually take no more than 10 minutes.

Even if you do not wish to be interviewed, we would still be able to use your questionnaire responses. For this we would ask you to complete the CAP-Knee scale at home on two different occasions, one week apart. We would send you a paper copy questionnaire including the CAP Knee scale to complete and return in a prepaid envelope. One week after you return the first completed questionnaire, you will receive another copy of the CAP-Knee scale to again complete and return in another prepaid envelope.

Expenses and payments

Participation in this study is entirely voluntary. Participants will not be paid to participate in the study. Travel expenses will be offered for any visits incurred as a result of participation in this study (on provision of receipts and up to a maximum of £20).

What are the possible disadvantages and risks of taking part?

We do not expect there are any important risks to you. We will try to minimise the inconvenience to you, and appreciate your time. During interviews sometimes people can find it difficult to talk about their pain experiences. Clinical knee examination will involve someone gently pressing on your knee and asking you to move it, and this might cause slight and momentary discomfort.

What are the possible benefits of taking part?

We do not expect the study to help you, although we do hope you will find it interesting. We expect that the information we get from this study may help improve treatment for people with knee pain in the future.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researcher who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this by contacting the Patient Advice and Liaison Service (PALS) on telephone: 0800 183 0204 or 01159249924; ext 654 or email: pals@nuh.nhs.uk.

Will my taking part in this study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, some parts of the data collected for the study will be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

All information which is collected about you during the course of the research will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database. Any information about you which leaves the hospital will have your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it.

Your personal data (address, telephone number) will be kept for up to 1 year after the end of the study so that we are able to contact you about the findings of the study and possible follow-up studies (unless you advise us that you do not wish to be contacted).

All other research data will be kept securely for at least 7 years to enable regulatory authorities to check that the study has been conducted properly. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team will have access to your personal data.

Although what you say in the interview is confidential, should you disclose anything to us which we feel puts you or anyone else at any risk, we may feel it necessary to report this to the appropriate persons.

What happens when the study stops?

A summary of our research findings will be made available on our website (http://www.nottingham.ac.uk/paincentre). If you agree, we may contact you about our research over the next few years. Otherwise, nothing new will be asked of you after you have completed this study.

What will happen if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw then the information collected so far cannot be erased and this information may still be used in the project analysis.

What will happen to the results of the research study?

The findings will be written up as a report, you would not be identifiable in any report or publication. We will use these findings to support the design of a large scale study to test the effectiveness of the developed questionnaire. A summary of the results will also be posted on our website (http://www.nottingham.ac.uk/paincentre) and will be available as a paper copy upon request. Please inform the researcher if you like to receive a copy of the research summary upon completion of the analysis.

Who is organising and funding the research?

The study is being organised by the University of Nottingham and is being funded by the Arthritis Research UK (ARUK).

Who has reviewed the study?

All research in the University of Nottingham is looked at by independent groups of people, called a Research Ethics Committee to protect your interests. The research study, materials, and interview schedule has been reviewed and approved by the Nottingham Research Ethics Committee 2.

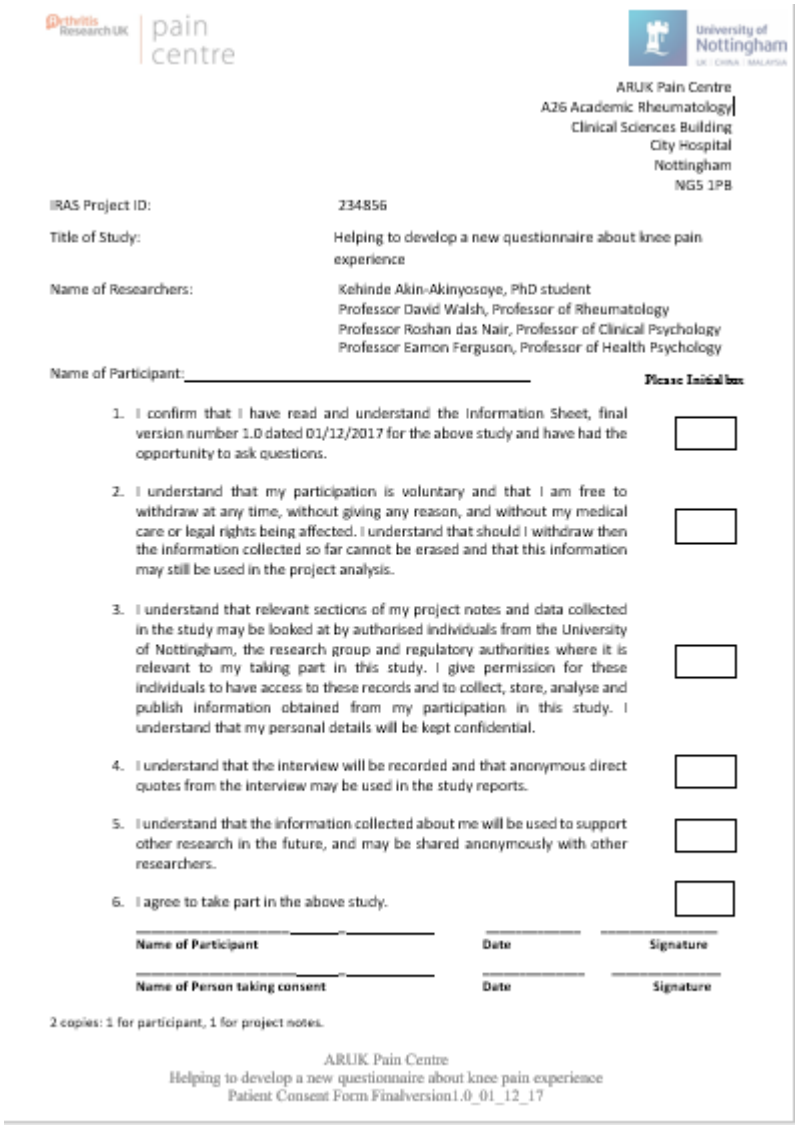
Further information and contact details

If you have any questions about the study, wish to discuss taking part or have any concerns, you can contact the researcher:

Professor David Walsh
A27 Academic Rheumatology
Clinical Sciences Building
City Hospital
Nottingham
NG5 1PB
Email: xxxxxxxx.xxxxxx@nottingham.ac.uk
Telephone: +44 (0)115 xxx xxxx

Many thanks for reading this information sheet.

Appendix 4.5. CAP-Knee Study Consent Form.



Arthritis Research UK | pain centre

University of Nottingham

ARUK Pain Centre
A26 Academic Rheumatology
Clinical Sciences Building
City Hospital
Nottingham
NG5 1PB

IRAS Project ID: 234856

Title of Study: Helping to develop a new questionnaire about knee pain experience

Name of Researchers: Kehinde Akin-Akinyosoye, PhD student
Professor David Walsh, Professor of Rheumatology
Professor Roshan das Nair, Professor of Clinical Psychology
Professor Eamon Ferguson, Professor of Health Psychology

Name of Participant:_____ **Please Initial box**

1. I confirm that I have read and understand the Information Sheet, final version number 1.0 dated 01/12/2017 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐
3. I understand that relevant sections of my project notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐
4. I understand that the interview will be recorded and that anonymous direct quotes from the interview may be used in the study reports. ☐
5. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers. ☐
6. I agree to take part in the above study. ☐

Name of Participant	**Date**	**Signature**
Name of Person taking consent	**Date**	**Signature**

2 copies: 1 for participant, 1 for project notes.

Appendix 5. Interview Guide for Cognitive Interview.

Introduction

“Hello, my name is Kehinde Akin-Akinyosoye. I am a PhD student with the Arthritis Research UK Pain Centre at Nottingham University. Thank you for agreeing to participate in this interview. Your feedback will help us learn how people with knee pain interpret the questions within this questionnaire. The purpose for this interview is to find out your understanding of each question, particularly, how you come to understand these questions.”

“I will be tape recording the interview. Do I have your permission to record the interview?”

- If yes, start the tape recorder and read the consent form (Appendix B) to the interviewee.
- If no, terminate the interview. Offer participant inclusion to the reliability study to the participant.

“Before we start, I just have a few things to tell you”.

“This interview will only take 30 minutes depending on how much you would like to say in answer to each question”

“If you would like to withdraw from the study and stop the interview at any time, then you can do so without giving a reason. If you would like to have a break during the interview, you are also free to do so. I will pause the audio recording at that point until we begin the interview again.”

“For this interview, I will hand you a blank version of the questionnaire. The questionnaire contains 8 questions which we will be discussing today. I will like you to complete this questionnaire, and I will then ask you about how you understood and responded to each question.

“Do you have any questions before we begin?”

- Answer any questions

- Hand over blank questionnaire to participant

“Please remember that there are no right or wrong answers, and what you say will not hurt my feelings. Feel free to say anything that you are thinking”

“Are you happy to go ahead with the interview?

- If yes, begin interview: “Okay, let’s begin with the first question”
- If no, ask: “Are there any concerns that you would like me to address?”

Question 1: Cold or heat touching my knee was painful

Probe:

- “Can you tell me in your own words, what the statement means to you?”

If participant shows difficulty responding: “Can you repeat the question I just asked in your own words?”

- “What were you thinking of when you answered the statement?”

If participant shows difficulty responding: “How did you go about deciding on which answer to pick?”

- “How sure are you of your answer?”

Question 2: I generally felt tired

Probe:

- “Can you tell me in your own words, what the statement means to you?”

If participant shows difficulty responding: “Can you repeat the question I just asked in your own words?”

- “What were you thinking of when you answered the statement?”

If participant shows difficulty responding: “How did you go about deciding on which answer to pick?”

- “How sure are you of your answer?”

Question 3: My knee pain stopped me concentrating on what I was doing

Probe:

- “Can you tell me in your own words, what the statement means to you?”

If participant shows difficulty responding: “Can you repeat the question I just asked in your own words?”

- “What were you thinking of when you answered the statement?”

If participant shows difficulty responding: “How did you go about deciding on which answer to pick?”

- “How sure are you of your answer?”

Question 4: I kept thinking about how much my knee hurts

Probe:

- “Can you tell me in your own words, what the statement means to you?”

If participant shows difficulty responding: “Can you repeat the question I just asked in your own words?”

- “What were you thinking of when you answered the statement?”

If participant shows difficulty responding: “How did you go about deciding on which answer to pick?”

- “How sure are you of your answer?”

Question 5: In general, I got sudden feelings of panic

Probe:

- “Can you tell me in your own words, what the statement means to you?”

If participant shows difficulty responding: “Can you repeat the question I just asked in your own words?”

- “What were you thinking of when you answered the statement?”

If participant shows difficulty responding: “How did you go about deciding on which answer to pick?”

- “How sure are you of your answer?”

Question 6: My knee pain affected my sleep

Probe:

- “Can you tell me in your own words, what the statement means to you?”

If participant shows difficulty responding: “Can you repeat the question I just asked in your own words?”

- “What were you thinking of when you answered the statement?”

If participant shows difficulty responding: “How did you go about deciding on which answer to pick?”

- “How sure are you of your answer?”

Question 7: I generally still enjoyed the things I used to enjoy

Probe:

- “Can you tell me in your own words, what the statement means to you?”

If participant shows difficulty responding: “Can you repeat the question I just asked in your own words?”

- ““What were you thinking of when you answered the statement?”

If participant shows difficulty responding: “How did you go about deciding on which answer to pick?”

- “How sure are you of your answer?”

Question 8: This final 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

Probe:

- “Can you tell me in your own words, what the statement means to you?”

If participant shows difficulty responding: “Can you repeat the question I just asked in your own words?”

- “What were you thinking of when you were shading in the picture?”

If participant shows difficulty responding: “How did you go about deciding on how to shade in the picture?”

- “Can you tell me how long have you felt pain in the areas that you shaded?”
- “How sure are you of your answer?”

Closing

“That was my final question. I will now switch of the audio recording equipment.”

Switch off recording equipment

“Thank you for taking time to answer these questions and for your participation in the study. Please feel free to share any other comments that you haven’t shared to this point”

- Pause to allow the interviewee to share additional comments.

“If there are questions or concerns, please contact me on 0115 823 1759.”

Appendix 6. Physical assessment form.

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Study ID:_____

Appointment Date: _____

Time: _____

Physical Assessment of the Knee

History

Knee pain	Do you have any knee pain on most days of the month? (Y/N)	
	If yes, where? (L/R/Both)	
Stiffness <30 minutes	Do you get stiffness in your knee as opposed to pain? (Y/N)	
	If yes, does that vary during the day? (Y/N)	
	If no, what are you like first thing in the morning?	
	How long does it take you to get your knee moving in the morning?	

On Examination	Left Knee (Y/N)	Right knee (Y/N)
Crepitus on active motion of the knee		
Bony tenderness		
Bony enlargement		
No palpable warmth		

To classify as having knee OA, individuals must report knee pain, plus 3 of the following 6: age>50years, stiffness, crepitus, Bony tenderness, bony enlargement, and no palpable warmth

Appendix 7. Coding Scheme.

Neuropathic- like pain:

Item:‘Cold or heat touching my knee was painful’

Definition:This question investigates hypersensitivity to heat or cold that is less extreme than would normally be required to cause pain or damage, indicative thermal allodynia (Phillips, Hopwood, Stroud, Dieppe, & Toms, 2017). Application of a cold or hot stimulus that would normally not cause pain when in physical contact with unaffected areas, causes pain to the individual’s knee.

Comprehension:

Completely aligned if:

- Respondent only referring to object or substance of a certain temperature “making contact with”, or “touching” or “put on” the knee.

Completely not aligned if:

- Respondent referring to increased or decreased pain due to hot or cold stimulus making contact with knee, and/or
- Respondent referring to stimuli which does not physically make contact with the knee (e.g. weather, or room temperature).

Partially aligned:

- Respondent referring to object or substance of a certain temperature “making contact with”, or “touching” or “put on” the knee; and
- Respondent referring to increased or decreased pain due to hot or cold stimulus making contact with knee; and/or
- Respondent referring to stimuli which does not physically make contact with the knee (e.g. weather, or room temperature).

Retrieval:

No Retrieval Difficulty if:

- Respondent only refers to event(s) related to the hot or cold stimuli causing, or not causing pain to the affected knee.

Complete Retrieval difficulty evident if:

- Respondent's only recollection of event(s) not related to hot or cold stimuli causing, or not causing pain to the affected knee

Partial Retrieval difficulty evident if:

- Respondent referring to event(s) related to the hot or cold stimuli causing, or not causing pain to the affected knee; and
- Respondent's recollection of event(s) not related to hot or cold stimuli causing, or not causing pain to the affected knee

Judgement:

(Applies to all items)

Certain initial response observed when:

- Respondent is certain of initial response provided before interview commenced; and
- Respondent response matches the retrieved memory for the item.

Uncertain initial response identified if:

- Respondent is unsure of initial response provided before interview commenced; and/or
- Mismatch between retrieval of memory and response provided. For example, a respondent describing painful heat or cold occurring once

in a while, but responds “never” on the questionnaire shows estimation difficulty; and/or

- Respondent is unable to decide on a response for the question.

Response:

(Applies to all items)

Consistent:

- Only one tick provided for the question

Inconsistent response:

- No ticks provided for the question; or
- More than two ticks provided as a response.

Fatigue:

Item: ‘I generally felt tired’

Definition:This item investigates the enduring, subjective sensation of generalized tiredness or exhaustion, which may or may not be related to knee pain. Fatigue, or feeling tired is typically also described as feeling “rundown” or “knackered”, physically and/or mentally. A previous qualitative study found that individuals with OA pain distinguish between physical and mental fatigue. Physical fatigue was described to be associated with aches and pains in limbs and muscle, while mental fatigue was described as “feeling drained” and “lacking focus” (Hawker et al., 2008).

Comprehension:

Completely aligned if:

- Respondent describing physical and/or mental elements of fatigue.
- Respondent referring to knee pain causing the feeling of fatigue.

Completely not aligned if:

- Respondent not describing physical and/or mental elements of fatigue.

Partially aligned:

- Respondent describing feeling related to both codes of complete alignment and completely not aligned comprehension of the item.

Retrieval:

No Retrieval Difficulty if:

- Respondent referring to event(s) related to feeling or not feeling fatigued. This recollection may or may not be based on activity induced fatigue, including knee activity.

Complete Retrieval difficulty evident if:

- Respondent's recollection of event(s) describing fatigue.
- Respondent's recollection of event(s) not describing feeling fatigued.

Partial Retrieval difficulty evident if:

- Respondent's recollection of event(s) both related and unrelated to feeling or not feeling fatigued.

Cognitive impact:

Item: ‘My knee pain stopped me concentrating on what I was doing’

Definition: Concentration is an attentional process that involves the ability to focus on the task at hand while ignoring distractions (Moran, 2012). Knee pain interferes with-, or interrupts-, or distracts-, or prevents- someone from concentrating on something they were previously focused on.

Comprehension:

Completely aligned if:

- Respondent describing having to “stop activity”, or “take a break” or “change activity” due to the knee pain.
- Such interruption could be relevant to active (e.g. working) or passive (e.g. while watching television) tasks.

Partially aligned:

- Respondent describing feeling related to both codes of complete alignment and completely not aligned comprehension of the item.

Completely not aligned if:

- Respondent describes interference of knee pain whilst “doing nothing” or not focusing on an activity such as walking.
- Respondent describes being ‘put off’ or not beginning a task due to knee pain or due to thoughts about the knee pain
- Respondent describes having to think about carrying out a task before commencement.

Retrieval:

No Retrieval Difficulty if:

- Respondent referring to event(s) related to knee pain interfering with concentration during active (e.g. working) or passive (e.g. while watching television) tasks.

Complete Retrieval difficulty evident if:

- Respondent's recollection of event(s) not related to knee pain interfering with concentration, or
- Respondent's recollection of event(s) related to

Partial Retrieval difficulty evident if:

- Respondent's recollection of event(s) both related and unrelated to cognitive impact codes of complete- and no- retrieval difficulty.

Catastrophizing:

Item: 'I kept thinking about how much my knee hurts'

Definition: This item investigates the focused attention on knee pain, on its possible causes and consequences, as opposed to its solutions, indicative of ruminative thoughts (Hilt, Sander, Nolen-Hoeksema, & Simen, 2007). This item seeks to identify the frequency of ruminative thoughts about having knee pain, and the knee pain experience.

Comprehension:

Completely aligned if:

- Respondent describing frequent or infrequent thoughts specific to the respondent's experience in having and/or living with knee pain (E.g.

"How painful the knee is", "How the knee pain has affected, or how the knee pain will affect them").

Completely not aligned if:

- Respondent describes thoughts not specific to their personal experience of having and/or living with knee pain.

Partially aligned if:

- Respondent describing feeling related to both codes of complete alignment and completely non-aligned comprehension of the item.

Retrieval:

No Retrieval Difficulty if:

- Respondent recollects event(s) related to ruminative thoughts about having knee pain, and the knee pain experience.

Complete Retrieval difficulty evident if:

Respondent's recollection of event(s) unrelated to ruminative thoughts about having knee pain, and the knee pain experience.

Partial Retrieval difficulty evident if:

- Respondent's recollection of event(s) both related and unrelated to ruminative thoughts about having knee pain, and the knee pain experience

Anxiety:

Item: 'In general, I got sudden feelings of panic'

Definition: Panic is an extreme form of fear and anxiety, and is characterized by physical sensations, such as a racing heart, shortness of breath that lasts

for a short period of time. Panic is defined as an inborn fear of unfamiliar situations, triggered by frightening thoughts, images, and sensations (Busch & Shapiro, 1993)This question seeks to identify whether the respondent has had feelings of panic, nervousness or unease, whether physical (e.g. racing heart) or mental (e.g. racing thoughts), which may or may not be related to knee pain.

Comprehension:

Completely aligned if:

- Respondent describing feelings related to panic that occur regardless of knee pain, or
- Respondent describes feelings of panic related to- or generated by the knee pain.

Completely not aligned if:

- Respondent describing feeling unrelated to panic

Partially aligned if:

- Respondent describing feeling related to both codes of complete alignment and completely non-aligned comprehension of the item.

Retrieval:

No Retrieval Difficulty if:

- Respondent recollects event(s) related to having feelings of panic, or anxiety, or nervousness.
- Respondent’s recollection of event(s) describing panic that is due to knee pain.

Complete Retrieval difficulty evident if:

- Respondent's recollection of event(s) unrelated to having feelings of panic.

Partial Retrieval difficulty evident if:

- Respondent's recollection of event(s) both related and unrelated to having feeling of panic or anxiety or nervousness, which may or may not be due to the knee pain.

Sleep:

Item: 'My knee pain affected my sleep'

Definition: This item investigates the frequency of knee pain disrupting sleep (nocturnal or daytime), including poor quality of sleep, insufficient or too much inefficient sleep, and interrupting sleep cycle.

Comprehension:

Completely aligned if:

- Respondent describing how sleep has been poor, interrupted or affected in one way or the other (e.g. uncomfortable in bed) due to their knee pain.

Completely not aligned if:

- Respondent describing generally being a poor sleeper, unrelated to the knee pain.

Partially aligned if:

- Respondent describing feeling related to both codes of complete alignment and completely non-aligned comprehension of the item.

Retrieval:

No Retrieval Difficulty if:

- Respondent recollects event(s) related to knee pain interrupting sleep cycle, sleep duration or sleep quality.

Complete Retrieval difficulty evident if:

- Respondent's recollection of event(s) unrelated to knee pain interrupting sleep cycle, sleep duration or sleep quality.

Partial Retrieval difficulty evident if:

- Respondent's recollection of event(s) both related and unrelated to knee pain affecting sleep

Depression:

Item: 'I generally still enjoyed the things I used to enjoy'

Definition: This depression item represents one of the key symptoms of major depression: a loss on interest or pleasure (Bartolomucci & Leopardi, 2009). This item investigates whether the respondent has had a noticeable loss of 'enjoyment' or 'pleasure' or 'satisfaction' or 'happiness' for previously enjoyed activities. Enjoyment is the feeling of pleasure and satisfaction that you have when you do or experience something that you like (Collins Dictionary).

Comprehension:

Completely aligned if:

- Respondent only refers to previously enjoyed activities and whether or not there has been any noticeable change in enjoyment for the referenced activities.

Completely not aligned if:

- Respondent only describing feelings unrelated to enjoyment of activities.

Partially aligned if:

- Respondent describing feeling related to both codes of complete alignment and completely non-aligned comprehension of the item.

Retrieval:

No Retrieval Difficulty if:

- Respondent only recollects event(s) related to enjoyment of activities, and how that has changed over time.

Complete Retrieval difficulty evident if:

- Respondent’s only recollection of event(s) are unrelated to enjoyment of activities; ordoes not take into consideration how the enjoyment of activities have changed over time.

Partial Retrieval difficulty evident if:

- Respondent‘s recollection of event(s) both related and unrelated to enjoyment of activities (i.e. respondent provides responses both

related to codes of ‘no retrieval difficulty’ and ‘complete retrieval difficulty’).

Pain distribution:

Item: ‘This final 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’

Definition: This question investigates location of pain across anatomical areas, as well as areas of ache and discomfort.

Comprehension:

Completely aligned if:

- Respondent only refers to ‘site’ or ‘location’ of pain anywhere on the body.

Not completely aligned if:

- Respondent only describes pain due to feverish illnesses; and/or
- Respondent describes pain that’s not occurring on most days of the month, or that occurred more than 4 weeks ago; and/or
- Respondent describes pain severity; and/or
- Respondent describes impact of pain; and/or
- Respondent describes cause of pain.

Partially aligned if:

- Respondent describing feeling related to both codes of complete alignment and completely non-aligned comprehension of the item.

Retrieval:

No Retrieval Difficulty if:

- Respondent only recollects event(s) related to origin, treatment, diagnosis and duration of painful sites on the body

Complete Retrieval Difficulty evident if:

- Respondent's only recollection of event(s) unrelated to painful sites; and/or
- Respondent describes pain only at the knee, despite previously discussing pain elsewhere
- Respondent describes pain at other sites, but not at the knee, despite previously discussing knee pain

Partial Retrieval difficulty evident if:

- Respondent's recollection of event(s) both related and unrelated to painful sites reported on item (i.e. respondent provides responses both related to codes of 'no retrieval difficulty' and 'complete retrieval difficulty').

Appendix 8. Expert consensus study: participant facing documents.

Appendix 8.1. Expert consensus study cover letter.

Kehinde Akin-Akinyosoye
Arthritis Research UK Pain Centre

Academic Rheumatology
University of Nottingham Clinical Sciences Building
City Hospital, Hucknall Road, Nottingham
NG5 1PB, United Kingdom
Tel. 00 44 115 823 1766
Fax. 00 44 115 823 1757

June 24, 2016

Dear [Insert name],

My name is Kehinde Akin-Akinyosoye; a PhD student working under the supervision Prof. Walsh and Prof. Ferguson within the Arthritis UK Pain Centre. I would be very grateful if you could participate in my research study focused on creating a clinical assessment tool to improve the use of pain relieving treatments in knee osteoarthritis. This current study fits into a major theme of the ARUK Pain Centre which seeks to maximize analgesia for established arthritis by mechanism-based stratified treatment.

I am currently seeking your expert opinion. I hypothesize that a person's reported experience of pain is determined by underlying pain mechanisms. Your contribution would help me to select questionnaire items that might reflect either predominantly peripheral or predominantly central pain mechanisms of knee osteoarthritis based on face validity. In this part of the study, questionnaire items have been shortlisted from those used in the Knee Pain in the Community (KPIC) questionnaire. Attachment 1 contains an information sheet which describes the working definition of peripheral and central pain mechanisms of knee OA pain used in the current project; as well as further instructions about the scoring method.

I ask that you complete the attached questionnaire (Attachment 2) by rating each item (ranging from "not at all", "slightly", "moderately" and "highly") in the Likert scales provided for each of peripheral and central mechanisms of knee OA pain. From test runs, I estimate this might take up to 30 minutes of your time. Once the questionnaire has been filled and returned, I shall tabulate the data, collate any comments to share with you, and your contribution to this study will be acknowledged. If you are willing and able to help with this, please return your completed questionnaire by July 8, 2016.

You have been invited due to your particular expertise and professional background, therefore, if you are unable to help with this part of our research at this stage, please let me know as soon as possible so that an alternative expert in your area can be contacted. A list of other members of the Pain Centre who have been invited to participate is also provided in Attachment 3.

Please for any further correspondence concerning this request and the current study, contact me at kehinde.akin@nottingham.ac.uk

Thank you for your consideration.

Sincerely,

Kehinde Akin-Akinyosoye.

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The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

ATTACHMENT 1: INFORMATION SHEET

Please rate each question within the attached questionnaire (attachment 2) on the scale *(ranging from "not at all", "slightly", "moderately" and "highly").*

The task that I would like you to perform is to **rate the extent to which response for each item classifies peripheral and central mechanisms of OA pain.** Please place a cross (X) in the box which most reflects your opinion for each scale.

Peripheral mechanisms of OA pain are defined for this purpose as **those processes occurring within the affected knee joint.** Examples of OA pain peripheral mechanisms might include nociception, mechanotransduction, peripheral nerve sensitisation, inflammation, joint damage, etc.

Central mechanisms of OA pain are defined for this purpose as those **processes occurring within the central nervous system.** Examples of OA pain central mechanisms might include, spinal nociceptive transmission, descending facilitation and inhibition, central sensitization at the spinal level or higher, and production or modulation of conscious pain (sensory-discriminative and affective aspects of pain response) within specific brain areas, etc.

Careful consideration should be taken before rating items within each scale. If an item is out of your area of expertise, please leave the item response blank.

Different 'experts' may reach different conclusions.

QUANTIFICATION OF EXPERT RATINGS

After completion of this rating exercise and ratings are returned from the experts, the Item-Content Validity Index (I-CVI) will be calculated and tabulated for each of the constructs (peripheral and central mechanisms).

$$\text{I-CVI (peripheral)} = \frac{\text{Number of Experts rating item as "moderately" or "highly" relevant (peripheral)}}{\text{Total number of experts}}$$

Lynn et al (1986) advised that when there are 6 or more experts, recommended I-CVI should be no lower than .78.

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ATTACHMENT 2: EXPERT QUESTIONNAIRE

Dear Dr. [name],

Based on your expert opinion, please use the scales below to **rate the extent to which response for each item classifies peripheral and central mechanisms of OA pain**. It is important that you carry out this task for each question in **BOTH** peripheral and central scales provided below.
Careful consideration should be taken before rating items within each scale. If an item is out of your area of expertise, please leave the item response blank.

		To what extent will item response classify **peripheral mechanisms**				To what extent will item response classify **central mechanisms**			
		Not at all	Slightly	Moderately	Highly	Not at all	Slightly	Moderately	Highly
1.	Over the past month, do you have a tingling or prickling sensation in the area of your most painful knee 'pain' (like crawling ants or electrical tingling)?	☐	☐	☐	☐	☐	☐	☐	☐
2.	Number of painful body regions (shaded on body pain manikin)	☐	☐	☐	☐	☐	☐	☐	☐
3.	In the past month. How intense was your worst knee pain rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'?	☐	☐	☐	☐	☐	☐	☐	☐
4.	How often during the past 4 weeks did you get enough sleep to feel rested in the morning?	☐	☐	☐	☐	☐	☐	☐	☐
5.	In the past month, did you feel tired on most days?	☐	☐	☐	☐	☐	☐	☐	☐

1

		To what extent will item response classify **peripheral mechanisms**				To what extent will item response classify **central mechanisms**			
		Not at all	Slightly	Moderately	Highly	Not at all	Slightly	Moderately	Highly
6.	Over the past month in your most painful knee, is light touching (clothing, a blanket) in this area painful?	☐	☐	☐	☐	☐	☐	☐	☐
7.	Please indicate how often the statement below applies to you: "I look forward with enjoyment to things"	☐	☐	☐	☐	☐	☐	☐	☐
8.	In your most painful knee, over the past month, is cold or heat (bath water) in this area occasionally painful?	☐	☐	☐	☐	☐	☐	☐	☐
9.	How much time during the past month did you have a lot of energy?	☐	☐	☐	☐	☐	☐	☐	☐
10.	In the past week, how upset or worried have you been by your knee pain that comes and goes?	☐	☐	☐	☐	☐	☐	☐	☐
11.	Please indicate what degree the statement below applies to your painful experience: "I can't seem it keep it out of my mind"	☐	☐	☐	☐	☐	☐	☐	☐

		To what extent will item response classify **peripheral mechanisms**				To what extent will item response classify **central mechanisms**			
		Not at all	Slightly	Moderately	Highly	Not at all	Slightly	Moderately	Highly
12.	In the past month, on average, how intense was the pain in your most painful knee rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'?	☐	☐	☐	☐	☐	☐	☐	☐
13.	Does your pain or other bodily symptoms stop you from concentrating on what you are doing?	☐	☐	☐	☐	☐	☐	☐	☐
14.	Does your pain or other bodily symptoms stop you from concentrating on what you are doing?	☐	☐	☐	☐	☐	☐	☐	☐
15.	Please indicate how often the statement below applies to you: "I still enjoy the things I used to enjoy"	☐	☐	☐	☐	☐	☐	☐	☐
16.	Please indicate what degree the statement below applies to your painful experience: "I keep thinking about how much it hurts"	☐	☐	☐	☐	☐	☐	☐	☐

		To what extent will item response classify **peripheral mechanisms**				To what extent will item response classify **central mechanisms**			
		Not at all	Slightly	Moderately	Highly	Not at all	Slightly	Moderately	Highly
17.	In the past week, how much has your constant knee pain affected your quality of life?	☐	☐	☐	☐	☐	☐	☐	☐
18.	Please indicate what degree the statement below applies to your painful experience: "I feel I can't stand it anymore"	☐	☐	☐	☐	☐	☐	☐	☐
19.	In the past week, how frustrated or annoyed have you been by your constant knee pain?	☐	☐	☐	☐	☐	☐	☐	☐
20.	Over the past month, do you suffer from a burning sensation (e.g., stinging nettles) in or around your most painful knee?	☐	☐	☐	☐	☐	☐	☐	☐
21.	Please indicate how often the statement below applies to you: "I can sit at ease and feel relaxed"	☐	☐	☐	☐	☐	☐	☐	☐
22.	Please indicate how often the statement below applies to you: "I get sudden feelings of panic"	☐	☐	☐	☐	☐	☐	☐	☐

		To what extent will item response classify **peripheral mechanisms**				To what extent will item response classify **central mechanisms**			
		Not at all	Slightly	Moderately	Highly	Not at all	Slightly	Moderately	Highly
23.	Please indicate what degree the statement below applies to your painful experience: "I feel I can't go on"	☐	☐	☐	☐	☐	☐	☐	☐
24.	How much time during the past month, have you felt calm or peaceful?	☐	☐	☐	☐	☐	☐	☐	☐

Appendix 8.4. Table showing profession of Expert panel included in Item generation study.

Expert Study Number	Profession
001	Genetic Epidemiologist
002	Consultant Orthopaedic Surgeon
003	Pain Researcher
004	Consultant Rheumatologist
005	Psychologist
006	Neuroscientist
007	Psychology
008	Pain Researcher
009	Neuroscientist
010	Consultant Rheumatologist
011	Consultant Rheumatologist
012	Physiotherapist
013	Physiotherapist
014	Pharmacist
015	Psychologist
016	Pain Researcher
017	Musculoskeletal Epidemiologist

Appendix 9. Supplementary findings supporting item generation chapter.

Appendix 9.1. Table showing standardized item loadings for competing four-factor model for emotional wellbeing item group.

Items	Factor 1	Factor 2	Factor 3	Factor 4
I feel tense or wound up	**0.033**	**0.380***	**0.412***	**0.188***
I still enjoy the things I used to enjoy	0.791*	-0.030	-0.058	0.002
I get a sort of frightened feeling as if something awful is about to happen	0.031	0.802*	0.084	-0.033
I can laugh and see the funny side of things	0.611*	0.021	0.231*	0.066***
Worrying thoughts go through my mind	-0.016	0.679*	0.261*	0.042
I feel cheerful	**0.589***	**-0.002**	**0.364***	**-0.002**
I can sit at ease and feel relaxed	**0.362***	**0.002**	**0.194****	**0.493***
I feel as if I am slowed down	**0.317***	**0.305***	**-0.305***	**0.013**

Table continued on next page
*p<0.001 **p<0.01 ***p<0.05
Rows in bold show cross loading items.
For the four-factor model, only one item showed acceptable loading (loading>0.3) on the fourth factor

Appendix 9.1. (*Cont.*). Table showing standardized item loadings for competing four-factor model for emotional wellbeing item group.

Items	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**
I get a sort of frightened feeling like 'butterflies' in the stomach	0.025	0.636*	-0.282*	-0.020
I have lost interest in my appearance	0.559*	0.095***	0.023	-0.022
I feel restless as if I have to be on the move	-0.037***	0.234*	-0.026	0.506*
I look forward with enjoyments to things	0.897*	0.023	0.002	-0.003
I get sudden feelings of panic	-0.020	0.821*	-0.002	0.121**
I can enjoy a good book or radio or television programme	**0.430***	**-0.050**	**-0.012**	**0.383***

*p<0.001 **p<0.01 ***p<0.05
Rows in bold show cross loading items.
For the four-factor model, only one item showed acceptable loading (loading>0.3) on the fourth factor.

Appendix 9.2. Table showing standardized item loadings for competing three-factor model for catastrophic thinking item group.

Items	Factor 1	Factor 2	Factor 3
I worry all the time about whether the pain will end	**0.337***	**0.171****	**0.387***
I feel I can‘t go on	0.925*	-0.014	-0.029
It’s terrible and I think it’s never going to get any better	0.762*	-0.10	0.209***
It’s awful and I feel that it overwhelms me	0.792*	0.143***	0.056
I feel I can’t stand it anymore	0.873*	0.094	-0.023
I become afraid that the pain will get worse	0.272*	-0.004	0.671*
I keep thinking of other painful events	**0.329***	**0.155*****	**0.371***
I anxiously want the pain to go away	-0.004	0.706*	0.204*
I can’t seem it keep it out of my mind	0.021	0.886*	0.024

Table continued on next page
*p<0.001 **p<0.01 ***p<0.05
Rows in bold show cross loading items.
For the three-factor model, only two items showed acceptable loading (loading>0.3) on the third factor

Appendix 9.2. (*Cont.*). Table showing standardized item loadings for competing three-factor model for catastrophic thinking item group.

Items	**Factor 1**	**Factor 2**	**Factor 3**
I keep thinking about how much it hurts	-0.104	1.000*****	-0.022
I keep thinking about how badly I want the pain to stop	0.055	0.828*****	0.070
There's nothing I can do to reduce the intensity of the pain	0.215*****	0.425*****	0.234******
I wonder whether something serious may happen	-0.002	0.175*******	0.640*****

*p<0.001 **p<0.01 ***p<0.05

Rows in bold show cross loading items.

For the three-factor model, only two items showed acceptable loading (loading>0.3) on the third factor.

Appendix 9.3. Table showing standardized item loadings for competing two-factor model in constant pain item group.

Items	Factor 1	Factor 2
In the past week, how intense has your constant knee pain been?	0.797*	0.165
In the past week, how much has your constant knee pain affected your sleep?	0.888*	-0.005*
In the past week, how much has your constant knee pain affected your overall quality of life?	**0.417***	**0.552***
In the past week, how frustrated or annoyed have you been by your constant knee pain?	0.184*	0.780*
In the past week, how upset or worried have you been by your constant knee pain?	-0.006*	0.940*

*p<0.001

Rows in bold show cross loading items.

For the two-factor model, only two items showed acceptable loading (loading>0.3) on either factor.

Appendix 9.4. Table showing standardized item loadings for competing two-factor model in intermittent pain item group.

Items	Factor 1	Factor 2
In the past week, how intense has your most severe knee pain that comes and goes been?	0.967*	-0.003
In the past week, how much has your knee pain that comes and goes affected your sleep?	0.709*	0.246**
In the past week, how much has your knee pain that comes and goes affected your overall quality of life?	**0.485***	**0.380***
In the past week, how frustrated or annoyed have you been by your knee pain that comes and goes?	**0.379***	**0.601***
In the past week, how upset or worried have you been by your knee pain that comes and goes?	0.215*	0.758*
In the past week, how frequently has this knee pain that comes and goes occurred?	-0.006*	0.946*

*p<0.001 ** p<0.05
Rows in bold show cross loading items.
For the two-factor model, only two items showed acceptable loading (loading>0.3) on the third factor.

Appendix 9.5. Table showing standardized item loadings for competing four-factor model in neuropathic-like pain item group.

Items	Factor 1	Factor 2	Factor 3	Factor 4
Over the past month, does your pain run up and down your leg?	0.218*	0.424*	0.033	0.113
How would you rate your most painful knee pain on a 0-10 scale at the present time, that is right now, where 0 is 'no pain' and 10 is 'pain as bad as could be'?	0.198*	0.350*	0.176**	-0.014
In the past month. How intense was your worst knee pain rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'?	0.674*	0.115**	0.138**	-0.091
In the past month, on average, how intense was the pain in your most painful knee rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'?	0.851*	-0.034	-0.021	0.199
The next question is on the pattern of your pain in your most painful knee. Which if the 4 different options below is the one that best describes the pattern of your worst knee pain over the past month?	0.940*	0.009	-0.004	0.037
Do you suffer from a burning sensation (e.g., stinging nettles) in or around your most painful knee?	0.077	0.610*	0.122	0.055

Table continued on next page
*p < 0.001 **p<0.05
Rows in bold show cross loading items.
For the four-factor model, no items showed acceptable loading (loading>0.3) on the fourth factor.

Appendix 9.5. (*Cont*.). Table showing standardized item loadings for competing four-factor model in neuropathic-like pain item group.

Items	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**
Do you have a tingling or prickling sensation in the area of your most painful knee 'pain' (like crawling ants or electrical tingling)?	-0.015	1.000*	-0.031	0.010
Is light touching (clothing, a blanket) in this area painful?	0.129*	0.169**	0.609*	-0.002
Do you have sudden pain attacks in the area of your pain, like electric shocks?	0.010	0.036	0.030	0.918
Is cold or heat (bath water) in this area occasionally painful?	-0.021**	-0.005	0.856*	0.028
Do you suffer from a sensation of numbness in the areas that you marked?	**-0.109****	**0.302***	**0.465***	**0.015**
Does slight pressure in this area, e.g., with a finger, trigger pain?	0.121**	-0.050	0.564*	0.031

*p < 0.001 **p<0.05
Rows in bold show cross loading items.
For the four-factor model, no items showed acceptable loading (loading>0.3) on the fourth factor.

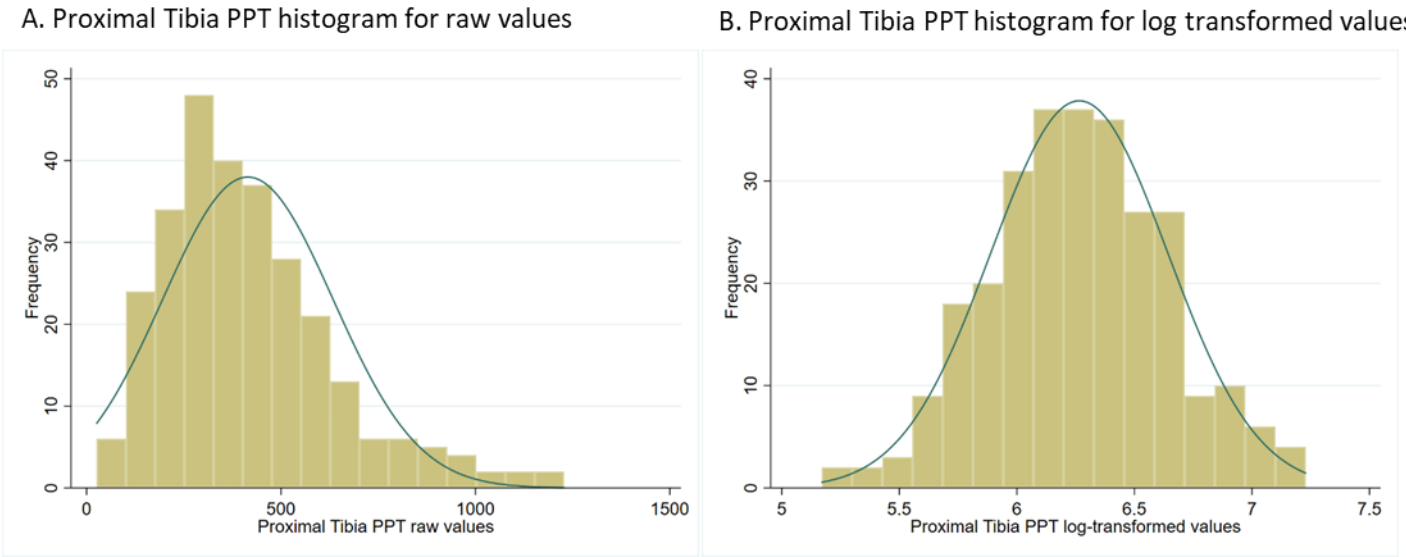
Appendix 9.6. Table showing standardized item loadings for competing two-factor model in fatigue/sleep item group.

Items	Factor 1	Factor 2
How often during the past 4 weeks did you get enough sleep to feel rested in the morning?	1.000*	-0.002**
How often during the past 4 weeks did you awaken short of breathe or with a headache?	0.019	0.550*
How often during the past 4 weeks did you have trouble falling asleep?	-0.204	0.374**
How often during the past 4 weeks did you have trouble staying awake during the day?	0.198	0.831*
In the past month, did you feel tired on most days?	0.108	0.783*
During the past month, Did you have a lot of energy?	-0.071	0.660*

*p<0.001 **p<0.01 ***p<0.05
For the two-factor model, only one item showed acceptable loading (loading>0.3) on the first factor.

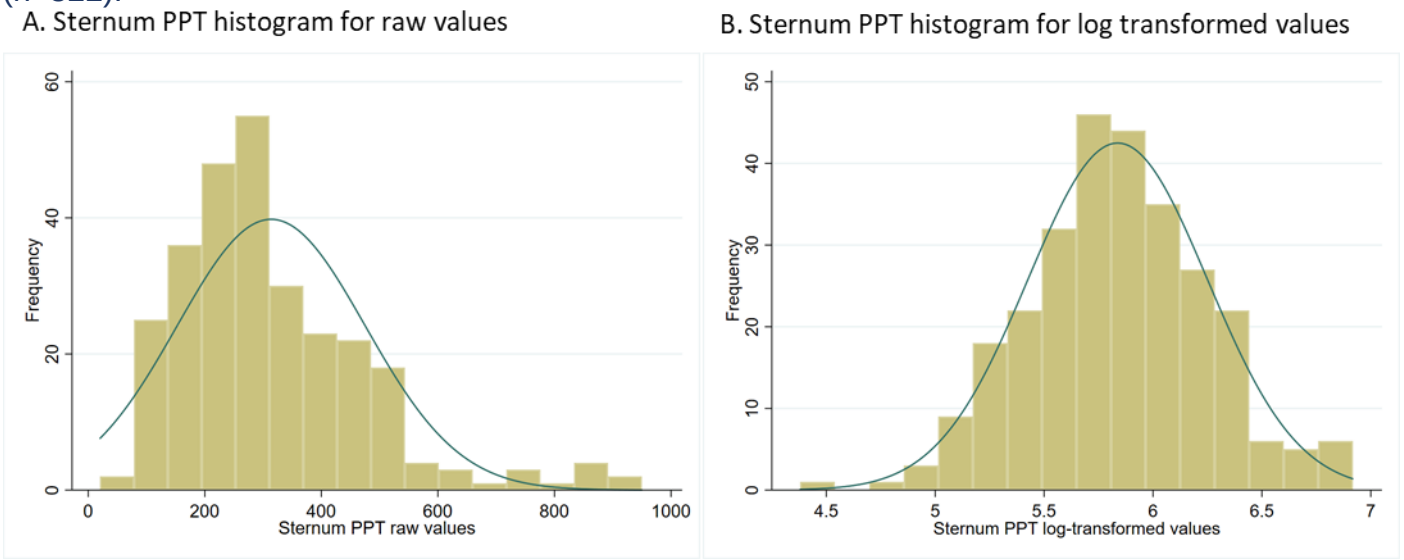
Appendix 10. Figures showing histograms for Pressure Pain Thresholds (PPTs) across all measured anatomical sites.

Appendix 10.1. Histograms for raw and log-transformed PPT values at the Proximal tibia of the index knee within baseline knee pain population (n=322).



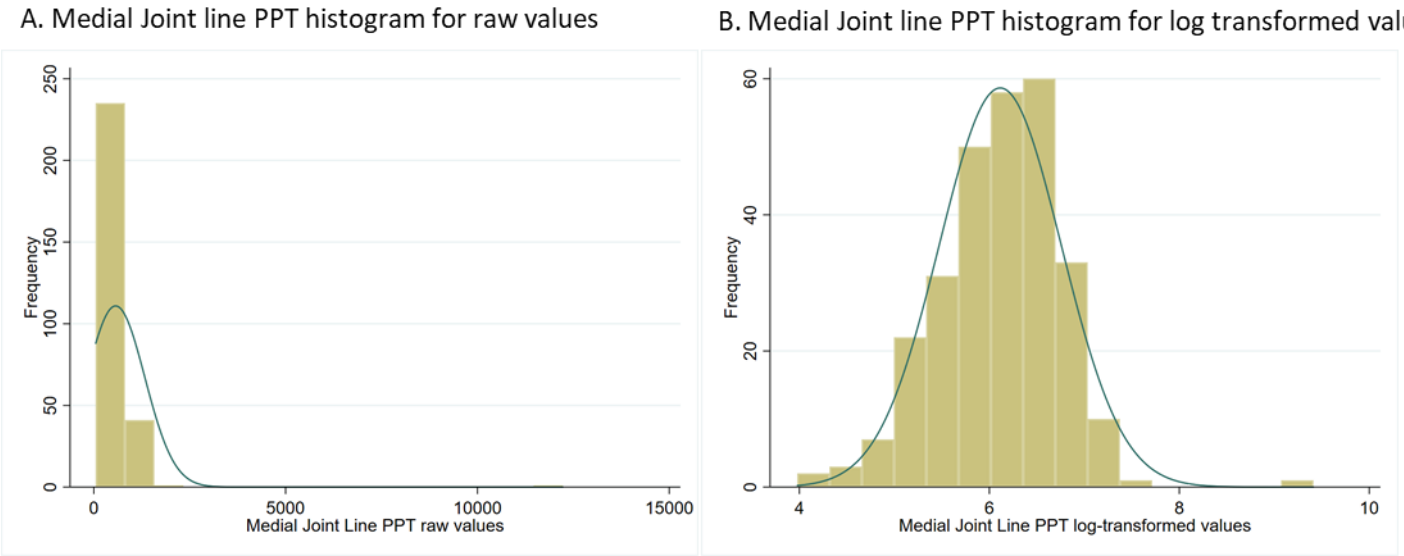
Histograms for **A**. Proximal Tibia PPT histogram for raw values (skewedness=1.06; kurtosis = 4.26; Shapiro Wilk's p-value < 0.00001); and **B.** Proximal Tibia PPT histogram for log transformed values (skewedness=-0.0000006; kurtosis = 2.93; Shapiro Wilk's p-value = 0.828). These suggest that skewed raw PPT values were normally distributed following log transformation.

Appendix 10.2. Histograms for raw and log-transformed PPT values at the Sternum within baseline knee pain population (n=322).



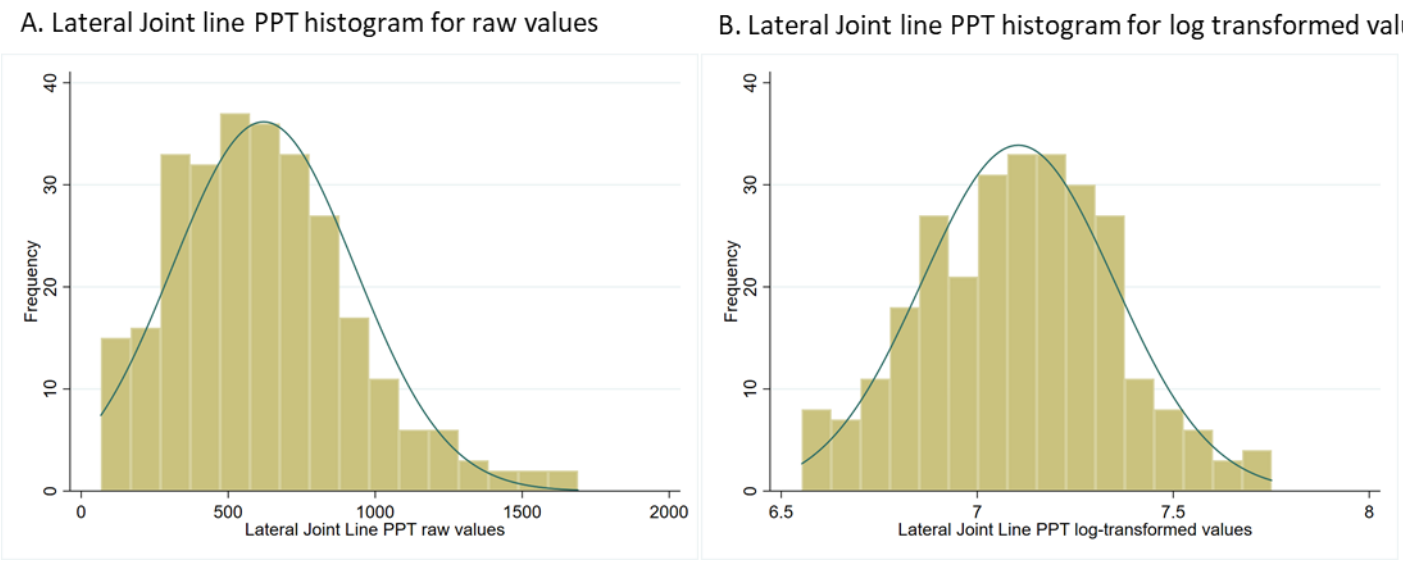
Histograms for **A**. Sternum PPT histogram for raw values (skewedness=1.32; kurtosis = 5.34; Shapiro Wilk's p-value < 0.00001); and **B.** Sternum PPT histogram for log transformed values (skewedness=-0.0000006; kurtosis = 3.20; Shapiro Wilk's p-value = 0.578). These suggest that skewed raw PPT values were normally distributed following log transformation.

Appendix 10.3. Histograms for raw and log-transformed PPT values at the medial joint line of the index knee within baseline knee pain population (n=322).



Histograms **for A.** Medial Joint line PPT histogram for raw values (skewedness=13.01; kurtosis = 199.73; Shapiro Wilk's p-value =0.898); and **B.** Medial Joint line PPT histogram for log transformed values (skewedness=0.0009; kurtosis = 5.03; Shapiro Wilk's p-value < 0.00001). These suggest that skewed raw PPT values were more normally distributed following log transformation.

Appendix 10.4. Histograms for raw and log-transformed PPT values at the lateral joint line of the index knee within baseline knee pain population (n=322).



Histograms for **A**. Medial Joint line PPT histogram for raw values (skewedness=0.61; kurtosis = 3.25; Shapiro Wilk's p-value =0.898; and **B**. Medial Joint line PPT histogram for log transformed values (skewedness=-0.00001; kurtosis = 2.72; Shapiro Wilk's p-value = 0.232. These suggest that skewed raw PPT values were normally distributed following log transformation.

Appendix 11. Supplementary findings supporting item selection chapter.

Appendix 11.1. Table showing Area Under the Curve (AUC) and details of cut off points for 7- and 23- site quantification on the body pain manikin.

	AUC	(95% CI)	Optimal cut-off point	Sensitivity (TPR)	Specificity (TNR)	Correctly Classified
7- site quantification						
Proximal Tibia	0.58 (0.48 – 0.67)		>=5	27.50%	81.09%	73.38%
Sternum	0.59 (0.49 – 0.69)		>=5	38.10%	82.98%	76.17%
Medial JL	0.59 (0.50 – 0.68)		>=5	29.17%	81.74%	72.66%
Lateral JL	0.62 (0.52 – 0.73)		>=5	34.29%	81.74%	75.47%

Table continued on next page
TPR = True Positive Rate
TNR = True Negative Rate

Appendix 11.1. (*Cont*.). Table showing Area Under the Curve (AUC) and details of cut off points for 7- and 23- site quantification on the body pain manikin.

	AUC	(95% CI)	Optimal cut-off point	Sensitivity (TPR)	Specificity (TNR)	Correctly Classified
23- site quantification						
Proximal Tibia	0.58 (0.48 – 0.67)		>=6	40.00%	74.79%	69.78%
Sternum	0.59 (0.49 – 0.69)		>=6	45.24%	75.74%	71.12%
Medial JL	0.58 (049 – 0.67)		>=6	37.50%	74.78%	68.35%
Lateral JL	0.61 (0.50 – 0.72)		>=6	42.86%	74.78%	70.57%

TPR = True Positive Rate
TNR = True Negative Rate

Appendix 11.2. Table showing inter-item correlation matrix for 19 items putatively reflecting central mechanisms in people with knee pain.

		Anxiety		**Depression**		**Neuropathic- like pain**			**Fatigue**	**Cognitive Impact**	**Pain Distribution**
Traits	Items	Fright	Panic	Still enjoy	Look forward	Tingling	Light touch	Cold heat	Tired	Concentrate on pain	Other pain below waist
Anxiety	Panic	0.66*	1.00	-	-	-	-	-	-	-	-
Depression	Still enjoy	0.19*	0.20*	1.00	-	-	-	-	-	-	-
	Look forward	0.32*	0.28*	0.56*	1.00	-	-	-	-	-	-
Neuropathic- like pain	Tingling	0.24*	0.20*	0.27*	0.20*	1.00	-	-	-	-	-
	Light touch	0.22*	0.29*	0.26*	0.23*	0.51*	1.00	-	-	-	-
	Cold/heat	0.21*	0.20*	0.25*	0.26*	0.47*	0.65*	1.00	-	-	-

Table continued on next page

Data are Spearman correlation coefficients from participants with knee pain (n=322). *p<0.05

Appendix 11.2. (*Cont.*). Table showing inter-item correlation matrix for 19 items putatively reflecting central mechanisms in people with knee pain.

		Anxiety		**Depression**		**Neuropathic- like pain**			**Fatigue**	**Cognitive Impact**	**Pain Distribution**
	Items	Fright	Panic	Still enjoy	Look forward	Tingling	Light touch	Cold heat	Tired	Concentrate on pain	Other pain below waist
Fatigue	Tired	0.41*	0.39*	0.33*	0.37*	0.23*	0.31*	0.33*	1.00	-	-
Cognitive Impact	Concentrate on pain	0.35*	0.33*	0.41*	0.38*	0.38*	0.41*	0.37*	0.44*	1.00	-
Pain Distribution	Other pain below waist	0.11	0.07	0.21*	0.24*	0.07	0.19*	0.13*	0.18*	0.29*	1.00
Pain Catastrophizing	Can't stand it	0.41*	0.34*	0.35*	0.43*	0.42*	0.29*	0.33*	0.36*	0.49*	0.11
	Can't go on	0.40*	0.32*	0.37*	0.44*	0.36*	0.31*	0.33*	0.32*	0.42*	0.11

Table continued on next page

Data are Spearman correlation coefficients from participants with knee pain (n=322). *p<0.05

Appendix 11.2 (*Cont.*). Table showing inter-item correlation matrix for 19 items putatively reflecting central mechanisms in people with knee pain.

		Anxiety		**Depression**		**Neuropathic- like pain**			**Fatigue**	**Cognitive Impact**	**Pain Distribution**
	Items	Fright	Panic	Still enjoy	Look forward	Tingling	Light touch	Cold heat	Tired	Concentrate on pain	Other pain below waist
Pain Catastrophizing	Out of mind	0.46*	0.40*	0.28*	0.44*	0.39*	0.33*	0.35*	0.38*	0.44*	0.17*
	Keep thinking	0.44*	0.39*	0.22*	0.41*	0.35*	0.38*	0.34*	0.33*	0.42*	0.19*
Constant pain experience	Sleep	0.17*	0.19*	0.27*	0.29*	0.45*	0.53*	0.51*	0.35*	0.48*	0.26*
	Frustrate	0.22*	0.18*	0.36*	0.32*	0.49*	0.42*	0.45*	0.35*	0.47*	0.24*
	Upset	0.26*	0.26*	0.31*	0.32*	0.49*	0.41*	0.41*	0.32*	0.45*	0.20*
Intermittent pain experience	Sleep	0.24*	0.26*	0.26*	0.30*	0.48*	0.53*	0.48*	0.33*	0.46*	0.26*
	Upset	0.26*	0.26*	0.29*	0.33*	0.49*	0.37*	0.42*	0.31*	0.45*	0.21*

Table continued on next page

Data are Spearman correlation coefficients from participants with knee pain (n=322). *p<0.05

Appendix 11.2 (*Cont.*). Table showing inter-item correlation matrix for 19 items putatively reflecting central mechanisms in people with knee pain.

		Pain Catastrophizing				**Constant pain experience**		**Intermittent pain experience**	
Traits	Items	Can't stand it	Can't go on	Out of mind	Keep thinking	Sleep	Frustrate	Upset	Sleep
Pain Catastrophizing	Can't stand it	1.00		-	-	-	-	-	-
	Can't go on	0.67*	1.00	-	-	-	-	-	-
	Out of mind	0.69*	0.53*	1.00	-	-	-	-	-
	Keep thinking	0.71*	0.51*	0.78*	1.00	-	-	-	-
Constant pain experience	Sleep	0.44*	0.32*	0.41*	0.43*	1.00	-	-	-
	Frustrate	0.52*	0.36*	0.50*	0.48*	0.67*	1.00	-	-
	Upset	0.47*	0.37*	0.51*	0.49*	0.60*	0.87*	1.00	-
Intermittent pain experience	Sleep	0.46*	0.33*	0.42*	0.44*	0.85*	0.63*	0.59*	1.00
	Upset	0.48*	0.39*	0.53*	0.51*	0.50*	0.78*	0.87*	0.54*

Data are Spearman correlation coefficients from participants with knee pain (n=322). *p<0.05.

Appendix 11.3. Table showing association between PPTs at sites other than the proximal tibia are predicted by ROC- derived and *a priori*- binary manikin classifications in individuals within the knee pain sample (n=322).

	Sternum			**Med JL**			**Lat JL**		
	b (95% CI)	β	p	b (95% CI)	β	p	b (95% CI)	β	p
Roc-Derived Classifications									
≥5/7 other sites	-0.20 (-0.37 to -0.03)	-0.18	0.002	-0.24 (-0.39 to -0.09)	-0.15	0.011	-0.29 (-0.47 to -0.12)	-0.19	0.001
≥6/23 other sites	-0.19 (-0.34 to -0.04)	-0.14	0.019	-0.16 (-0.30 to -0.03)	-0.14	0.018	-0.21 (-0.36 to -0.05)	-0.15	0.010
A priori Classifications									
Above waist	-0.08 (-0.22 to -0.06)	-0.05	0.430	-0.05 (-0.17 to 0.07)	-0.08	0.205	-0.08 (-0.22 to 0.06)	-0.07	0.266
Below waist	-0.17 (-0.30 to -0.03)	-0.16	0.007	-0.27 (-0.42 to -0.12)	-0.21	0.001	-0.22 (-0.36 to -0.08)	-0.18	0.002

Table continued on next page

Classifications are based on number or distribution of painful sites in addition to knee pain reported by participants on a body manikin. [a]Widespread pain; classified according to American College of Rheumatology criteria[37], including knee pain. Bold indicates statistically significant associations. ROC; receiver-operating curve. Log-transformed pressure pain detection thresholds (PPT) at (medial or lateral tibiofemoral joint line (JL), or remote (sternum) from the index knee reported here. Data utilized from knee pain sample (n=322). Unstandardized (b) and standardized (β) regression coefficients are presented.

Appendix 11.3. (*Cont.*) Table showing association between PPTs at sites other than the proximal tibia are predicted by ROC-derived and a priori- binary manikin classifications in individuals within the knee pain sample (n=322).

	Sternum			**Med JL**			**Lat JL**		
	b (95% CI)	β	p	b (95% CI)	β	p	b (95% CI)	β	p
Contralateral to index knee	-0.14 (-0.28 to 0.002)	-0.08	0.165	-0.18 (-0.34 to 0.03)	-0.14	0.021	-0.12 (-0.27 to 0.02)	-0.09	0.100
Axial pain	-0.01 (-0.15 to 0.12)	-0.05	0.441	-0.08 (-0.23 to 0.07)	-0.06	0.318	-0.07 (-0.21 to 0.07)	-0.06	0.309
ACR's Widespread pain[a]	-0.10 (-0.34 to 0.14)	-0.05	0.407	-0.09 (-0.39 to 0.20)	-0.04	0.533	0.01 (-0.22 to 0.25)	0.007	0.910

Classifications are based on number or distribution of painful sites in addition to knee pain reported by participants on a body manikin. [a]Widespread pain; classified according to American College of Rheumatology criteria[37], including knee pain. Bold indicates statistically significant associations. ROC; receiver-operating curve. Log-transformed pressure pain detection thresholds (PPT) at (medial or lateral tibiofemoral joint line (JL), or remote (sternum) from the index knee reported here. Data utilized from knee pain sample (n=322). Unstandardized (b) and standardized (β) regression coefficients are presented.

Appendix 11.4. Table showing associations between latent `Central mechanisms' trait and PPTs for sites other than proximal tibia within the knee pain sample (n=322).

	Sternum			**Medial JL**			**Lateral JL**		
	β	S.E	P	β	S.E	P	β	S.E	P
Unadjusted Model	-0.25	0.06	<0.001	-0.41	0.06	<0.001	-0.39	0.06	<0.001
Model adjusted for each questionnaire below:									
Constant Pain experience - ICOAP	-0.22	0.07	0.001	-0.32	0.06	<0.001	-0.29	0.07	<0.001
Neuropathic- like pain - PainDETECT	-0.22	0.06	0.001	-0.31	0.07	<0.001	-0.30	0.07	<0.001
Catastrophizing - PCS	-0.21	0.07	0.003	-0.38	0.07	<0.001	-0.34	0.07	<0.001
Anxiety - HADS	-0.20	0.07	0.003	-0.37	0.06	<0.001	-0.35	0.06	<0.001
Depression - HADS	-0.19	0.07	0.008	-0.42	0.07	<0.001	-0.37	0.07	<0.001

The single latent traitidentified through the 8 selected items, interpreted as `central mechanisms of knee pain', was associated with log-transformed pressure pain detection thresholds (PPT) at (medial or lateral tibiofemoral joint line (JL), or remote (sternum) from the index knee in an unadjusted model, and in models where total scores derived from each of the originating questionnaires (questionnaire summary score minus selected item) were adjusted for.
Standardized regression coefficients (β) presented.

Appendix 12. Supplementary findings supporting predictive validity chapter.

Appendix 12.1. Table showing correlation matrix for characteristics measured at baseline in people with knee pain.

		PPTs at index knee (n=204)				
		Proximal tibia	Sternum	Medial Joint Line	Lateral Joint Line	Radiographic severity (n=204)
PPTs at index knee	Sternum	0.70***	1.00	-	-	-
	Medial Joint Line	0.68***	0.71***	1.00	-	-
	Lateral Joint Line	0.75***	0.71***	0.83***	1.00	-
Radiographic severity		-0.03	0.04	0.04	-0.03	1.00
Self-report traits	Central Mechanisms trait (*Factor score*)	-0.25** (-0.24**)	-0.21** (-0.21***)	-0.37*** (-0.37***)	-0.35*** (-0.33***)	0.15* (0.15*)
	Pain Catastrophizing	-0.16*	-0.15	-0.23**	-0.24**	0.49*
	Anxiety	-0.18*	-0.19*	-0.26***	-0.25**	-0.11

Table continued on next page.

Data are unadjusted Spearman correlation coefficients from participants with knee pain. *p<0.05. **p<0.01 ***p<0.001

***** Measured by single items. Pain Distribution measured on the body pain manikin is coded as present when individual reports knee pain plus, other pain below the waist.

Appendix 12.1. (*Cont*.) Table showing correlation matrix for characteristics measured at baseline in people with knee pain.

		PPTs at index knee (n=204)				
		Proximal tibia	Sternum	Medial Joint Line	Lateral Joint Line	**Radiographic severity (n=204)**
Self-report traits	Depression	-0.13	-0.13	-0.19*	-0.21**	0.45*
	Sleep*	-0.24**	-0.15	-0.34***	-0.29***	0.46**
	Pain Distribution*+	-0.15*	-0.11	-0.24**	-0.23***	0.06
	Cognitive impact*	-0.15	-0.16*	-0.26***	-0.22**	0.24
	Fatigue*	-0.20**	-0.17*	-0.29***	-0.26***	0.03
	NP-like symptoms	-0.21*	-0.15	-0.28**	-0.28**	0.58***
Symptom duration		-0.13	-0.08	-0.12	-0.15*	0.45*

Table continued on next page.

Data are unadjusted Spearman correlation coefficients from participants with knee pain. *p<0.05. **p<0.01 ***p<0.001

***** Measured by single items. Pain Distribution measured on the body pain manikin is coded as present when individual reports knee pain plus, other pain below the waist.

Appendix 12.1. (*Cont.*). Table showing Correlation matrix for characteristics measured at baseline in people with knee pain.

		Central Mechanisms trait (Factor score)	Pain Catastrophizing	Anxiety	Depression	Sleep*	Pain Distribution*+	Cognitive impact*	Fatigue*
Self-report traits	Pain Catastrophizing	0.71*** (0.75***)	1.00	-	-	-	-	-	-
	Anxiety	0.64*** (0.66***)	0.55***	1.00	-	-	-	-	-
	Depression	0.69*** (0.72***)	0.57***	0.62***	1.00	-	-	-	-
	Sleep*	0.60*** (0.61***)	0.40***	0.28***	0.30***	1.00	-	-	-
	Pain Distribution*+	0.62*** (0.39***)	0.24***	0.19***	0.27***	0.22***	1.00	-	-

Table continued on next page.

Data are unadjusted Spearman correlation coefficients from participants with knee pain. *p<0.05. **p<0.01 ***p<0.001

***** Measured by single items. Pain Distribution measured on the body pain manikin is coded as present when individual reports knee pain plus, other pain below the waist.

Appendix 12.1. (*Cont*.). Table showing Correlation matrix for characteristics measured at baseline in people with knee pain.

	Central Mechanisms trait (Factor score)	Pain Catastrophizing	Anxiety	Depression	Sleep*	Pain Distribution*+	Cognitive impact*	Fatigue*
Cognitive impact*	0.72*** (0.83***)	0.56***	0.48***	0.56***	0.42***	0.31***	1.00	-
Fatigue*	0.65*** (0.68***)	0.43***	0.49***	0.53***	0.31***	0.26***	0.47***	1.00
NP-like symptoms	0.49*** (0.49***)	0.36***	0.35***	0.30***	0.43***	0.18***	0.35***	0.25***
Symptom duration	-0.13*** (-0.24**)	0.13***	0.10***	0.04	0.09**	0.12***	0.06*	0.13***

Data are unadjusted Spearman correlation coefficients from participants with knee pain. *p<0.05. **p<0.01 ***p<0.001
***** Measured by single items. Pain Distribution measured on the body pain manikin is coded as present when individual reports knee pain plus, other pain below the waist.

Appendix 12.2. Table showing prediction of pain persistence and persistent pain severity by derived Central Mechanisms trait factor scores independent of individual traits excluded from derived score.

Traits	**Prediction of pain persistence**		**Prediction of persistent pain severity**	
	RR (95% CI)	p	β (95% CI)	p
Central Mechanisms trait (all items)	**1.69 (1.49; 1.93)**	**<0.001**	**0.49 (0.43; 0.55)**	**<0.001**
Derived Central Mechanisms trait score adjusted for…:				
Excluded Neuropathic-like symptoms item	**1.40 (1.21; 1.61)**	**<0.001**	**0.39 (0.33; 0.45)**	**<0.001**
Excluded Catastrophizing item	**1.53 (1.31; 1.78)**	**<0.001**	**0.32 (0.25; 0.39)**	**<0.001**
Excluded Anxiety item	**1.62 (1.41; 1.88)**	**<0.001**	**0.51 (0.45; 0.57)**	**<0.001**
Excluded Depression item	**1.67 (1.43; 1.94)**	**<0.001**	**0.46 (0.39; 0.52)**	**<0.001**

Table Continued on Next Page.
Rows in bold indicate significant associations (p<0.05). Standardised coefficients for Risk Ratio (RR) and beta (β) are reported.
Derived scores for the Central Mechanisms trait (Central Mechanisms trait score minus item score for the selected individual trait) was associated with persistent knee pain after adjusting for the excluded trait score.
[+]Pain Distribution measured on the body pain manikin is coded as present when individual reports knee pain plus, other pain below the waist

Appendix 12.2. (*Cont*.). Table showing prediction of pain persistence and persistent pain severity by derived Central Mechanisms trait factor scores independent of individual traits excluded from derived score.

	Prediction of pain persistence		**Prediction of persistent pain severity**	
Derived Central Mechanisms trait score adjusted for…:	RR (95% CI)	p	β (95% CI)	p
Excluded Pain Distribution item⁺	**1.66 (1.44; 1.92)**	**<0.001**	**0.50 (0.45; 0.56)**	**<0.001**
Excluded Fatigue item	**1.93 (1.61; 2.32)**	**<0.001**	**0.59 (0.51; 0.67)**	**<0.001**
Excluded Sleep item	**1.24 (1.07; 1.43)**	**<0.001**	**0.20 (0.14; 0.26)**	**<0.001**

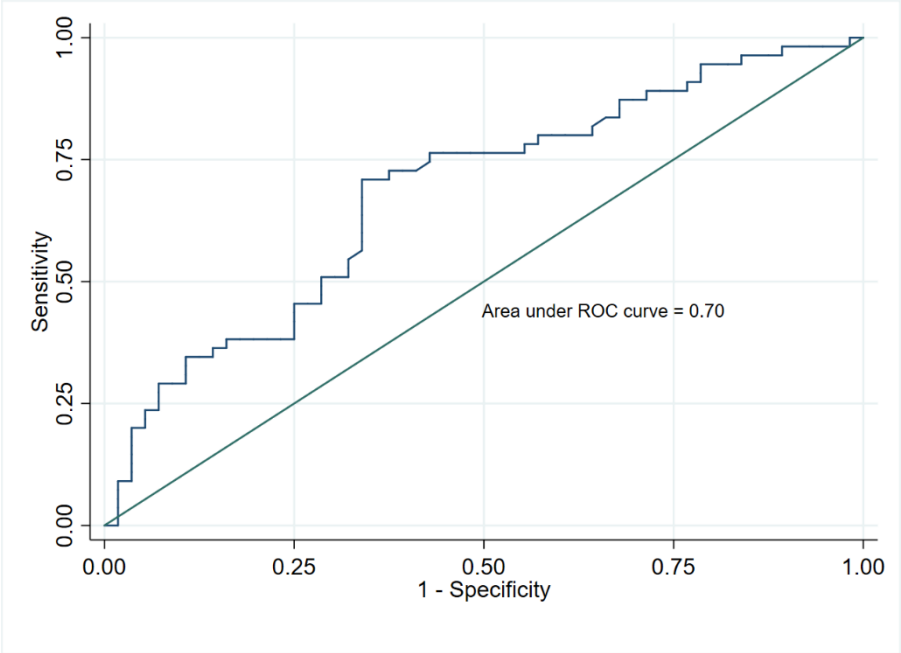
Rows in bold indicate significant associations (p<0.05). Standardised coefficients for Risk Ratio (RR) and beta (β) are reported.
Derived scores for the Central Mechanisms trait (Central Mechanisms trait score minus item score for the selected individual trait) was associated with persistent knee pain after adjusting for the excluded trait score.
⁺Pain Distribution measured on the body pain manikin is coded as present when individual reports knee pain plus, other pain below the waist.

Appendix 12.3. Table showing prediction of pain persistence and persistent pain severity by baseline Central Mechanisms trait factor scores independent of PPT scores.

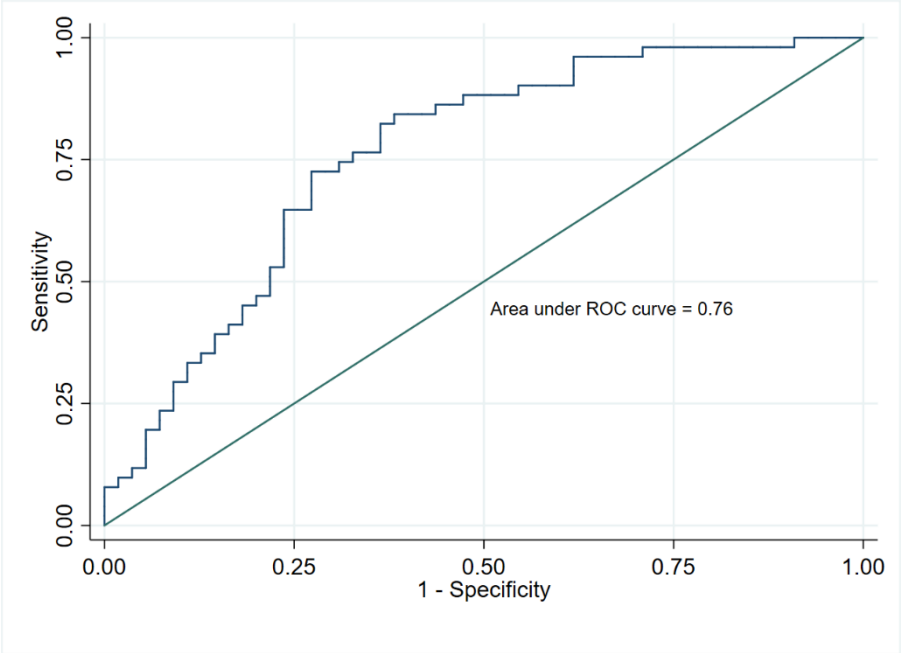
	Pain persistence		**Persistent pain severity**	
Traits	RR (95% CI)	p	β (95% CI)	p
Central Mechanisms	**1.69 (1.49; 1.93)**	**<0.001**	**0.49 (0.43; 0.55)**	**<0.001**
Central Mechanisms trait score adjusted for PPTs				
Proximal tibia PPT (kPa)	**1.99 (1.36; 2.93)**	**<0.001**	**0.66 (0.46; 0.86)**	**<0.001**
Sternum PPT (KPa)	**2.03 (1.38; 2.98)**	**<0.001**	**0.66 (0.46; 0.86)**	**<0.001**
Medial Joint Line (KPa)	**1.90 (1.28; 2.83)**	**0.001**	**0.66 (0.45; 0.87)**	**<0.001**
Lateral Joint Line (KPa)	**1.94 (1.31; 2.88)**	**0.001**	**0.65 (0.43; 0.86)**	**<0.001**

Rows in bold indicate significant associations (p<0.05)
Associations between Central Mechanisms trait scores and pain outcomes were adjusted for PPT scores.
Standardised coefficients for Risk Ratio (RR) and beta (β) reported.

Appendix 12.4. Figure showing Receiver Operating Characteristic (ROC) curve for prediction of pain persistence by Central Mechanisms trait factor scores in unadjusted and adjusted models.



Crude ROC curve



Adjusted ROC curve
(Model adjusted for age, sex, BMI, radiographic OA severity and symptom duration)

Appendix 13. Supplementary findings supporting CAP-Knee development chapter.

Appendix 13.1. Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Anxiety item.

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
Anxiety	Comprehension	Completely aligned	21/22 (95%)	"Do they get scared?" – Interview 14
("In general, I got sudden feelings of panic")		Partially aligned	1/22 (5%)	"Well I don't know what you mean by panic?... Panic is like a panic attack of some description- **Interviewer** What kind of behaviours would you associate with panicking? **Respondent** Like palpitations and things like that. – Interview 19
		Completely not aligned	0/22 (0%)	N/A
	Retrieval	No retrieval difficulty	22/22 (100%)	"No, the only time I panicked was, like I say, when I got a trapped nerve and I was thinking oh god what do I do." – Interview 18
		Partial Retrieval difficulty	0/22 (0%)	N/A
		Complete Retrieval difficulty	0/22 (0%)	N/A

Appendix 13.1. (*Cont.*). Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Anxiety item.

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
Anxiety **("In general, I got sudden feelings of panic")**	Judgement	Certain initial response	21/22 (95%)	"I'm, yeah, confident of that one, yeah" – Interview 21
		Uncertain initial response	0/22 (0%)	N/A
	Response selection	Consistent response	22/22 (100%)	N/A
		Inconsistent response	0/22 (0%)	N/A

Appendix 13.2. Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Depression item.

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
Depression ("I generally still enjoyed the things I used to enjoy")	Comprehension	Completely aligned	22/22 (100%)	"I used to enjoy things but I just don't take the chance anymore because the pain's so bad, so." – Interview 15
		Partially aligned	0/22(0%)	N/A
		Completely not aligned	0/22 (0%)	N/A
	Retrieval	No retrieval difficulty	22/22 (100%)	"And I used to love walking, go for long walks, but I can't do that now because of my knee" – Interview 20
		Partial Retrieval difficulty	0/22 (0%)	N/A
		Complete Retrieval difficulty	0/22 (0%)	N/A

Appendix 13.2. (*Cont.*). Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Depression item.

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
Depression ("I generally still enjoyed the things I used to enjoy")	**Judgement**	Certain initial response	19/22 (86%)	"Yeah, that's how I think I would act, how I do act, yeah." – Interview 11
		Uncertain initial response	3/22 (14%)	"Yeah, I put often, but I'm not sure if it's just sometimes. I don't know. I don't want to be negative." – Interview 12
	Response selection	Consistent response	22/22 (100%)	N/A
		Inconsistent response	0/22 (100%)	N/A

Appendix 13.3. Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Catastrophizing item.

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
Catastrophizing ("I kept thinking about how much my knee hurts")	Comprehension	Completely aligned	21/22 (95%)	"Well when it really takes over. You know, takes over your life, and you can't really think of anything else." – Interview 4
		Partially aligned	1/22 (5%)	"Um, well if I was watching you and I could see that you couldn't straighten your legs or something or you were limping then I would say 'is your leg hurting you, how much is it hurting'" – Reference #1, Interview 11 "Well I do sometimes because sometimes it kind of hurts more at times than it does other times. And I think well why is it hurting me like this as much now. It just hurts more sometimes than others and it makes me wonder what I have done, yeah." – Reference #2, Interview 11
		Completely not aligned	0/22 (0%)	N/A

Appendix 13.3. (*Cont.)*. Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Catastrophizing item.

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
Catastrophizing ("I kept thinking about how much my knee hurts")	Retrieval	No retrieval difficulty	22/22 (100%)	"Um, well if I'm sitting in, say I'm relaxing, and if I move my leg over it'll start hurting so I'm thinking about, you know, I've got to keep still, you know, I've got to get up and wash the pots! It's going to hurt then, you know, yeah. And if I've got to go down to the shop I'm thinking well will I be OK, will I get there alright, you know, so."– Interview 21
		Partial Retrieval difficulty	0/22 (0%)	N/A
		Complete Retrieval difficulty	0/22 (0%)	N/A

Appendix 13.3. (*Cont*.). Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Catastrophizing item.

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
Catastrophizing ("I kept thinking about how much my knee hurts")	Judgement	Certain initial response	20/22 (91%)	"I'm sure of that one, yeah." – Interview 2
		Uncertain initial response	2/22 (9%)	"**Interviewer** Are you sure that it's 'always'? **Respondent** Put 'sometimes', it hurts – Interview 13
	Response selection	Consistent response	22/22 (100%)	N/A
		Inconsistent response	0/22 (100%)	N/A

Appendix 13.4. Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Cognitive impact item.

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
Cognitive impact ("Knee pain stopped me concentrating on what I was doing")	Comprehension	Completely aligned	11/22 (54%)	"I've got to stop what I'm doing and go and take painkillers or I walk round a little bit to try and ease the pain in my knee" – Interview 7
		Partially aligned	4/22 (14%)	"Yeah, well, if I am concentrating on doing something, probably watching TV or I think most of the time I do have trouble with it, it's not when I'm walking on it so much, it's when I'm resting, when I get home, I'm doing this rubbing of my leg and that. It's more when I'm resting, it does play up more somehow, I don't know how that happens." – Interview 5
		Completely not aligned	7/22 (32%)	"How does the knee pain affect your everyday life then." – Interview 20
	Retrieval	No retrieval difficulty	8/22 (36%)	"I love growing things and I can't concentrate to kneel and to do it. It's a case of wait, stop, and I might stop at a point whereby I shouldn't stop for the plants' sake, you know."– Interview 1

Appendix 13.4. (C*ont*.).Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Cognitive impact item.

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
	Retrieval	Partial Retrieval difficulty	10/22 (45%)	"you're driving and then you get that knee pain and you think oh my goodness, in the leg, and it does actually, you try to concentrate on what you're doing and then you're thinking of the pain in the knee, so it does actually, yeah, stop you concentrating." Reference #1, Interview 7. "I have had occasions when I've been walking and my leg sort of, sometimes it just gives way with the pain, sometimes that does happen as well when I'm walking and that's sort of made me think ooh." Reference #2, Interview 7.
		Complete Retrieval difficulty	5/22 (23%)	"Well it could be walking and it gives you such a jump, you know, and then it makes it more like peg leg, you know, when the pain's – if I go still and the pain, well it usually goes stiff and it starts to ache and you can't bend it properly, so you're walking like Long John Silver off a peg leg."- Interview 22

Appendix 13.4. (*Cont.*).Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Cognitive impact item.

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
	Judgement	Certain initial response	21/22 (95%)	"I put never, and yeah, I'm sure about that one, yeah. I don't let it. I don't let it." – Interview 4
		Uncertain initial response	1/22 (5%)	**Interviewer** Alright, OK. So it's not really stopped you concentrating on what you were doing last week? **Respondent** No, no, to be honest. **Interviewer** So you replied 'sometimes' to that answer. **Respondent** Mm-hm. Interviewer And how sure are you of that response? **Respondent** It's good, yeah. - Interview 17
	Response selection	Consistent response	22/22 (100%)	N/A
		Inconsistent response	0/22 (0%)	N/A

Appendix 13.5. Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Sleep item.

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
Sleep ("Knee pain affected my sleep")	Comprehension	Completely aligned	18/22 (82%)	"It means is it waking me up?" – Interview 3
		Partially aligned	4/22 (18%)	"Yes, yeah – I don't sleep very well anyway, and I have sleeping pills, but it's difficult to get comfortable in bed." – Reference #1 Interview 12 "No, it doesn't wake me up" – Reference #2 Interview 12
		Completely not aligned	0/22 (0%)	N/A
	Retrieval	No retrieval difficulty	15/22 (68%)	"Can wake you up. I don't know why it is because you're resting your body and, you know, or if you turn, if you want to turn over, the pain kicks in, so then you've got to get comfortable again, yeah, sometimes two or three – I think one day I slept right through so I weren't too bad, then another day it can be two or three times it'll wake you up in the night." – Interview 22

Appendix 13.5. (*Cont.*).Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Sleep item.

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
Sleep ("Knee pain affected my sleep")	Retrieval	Partial Retrieval difficulty	6/22 (27%)	"Yeah, it has done for, like I say, with this knee especially, with the trapped nerve, I had to sleep with a pillow under my knee because I couldn't get comfortable. -" – Reference #1, Interview 18 "Well I know I've got arthritis in my left shoulder and I believe I've got it in my right as well. So that's mostly when I get up in the morning, like I say, when I sleep, if I sleep too long on it it goes over - I've got arthritis in my neck as well. So that traps a nerve in the neck and deadens my hand. I have that mostly first thing in the morning, I've got to keep going like that…" – Reference #2, Interview 18
		Complete Retrieval difficulty	1/22 (5%)	" Yeah. I wake up – maybe that is possibly because I don't sleep – I don't go to bed at 10 o'clock and I sleep through until, or whatever. I'm not that – I wake up during the night. Most nights. And then I just – you know, you just fidget around, whatever" - Interview 2

Appendix 13.5. (*Cont.*).Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Sleep item.

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
Sleep ("Knee pain affected my sleep")	Judgement	Certain initial response	20/22 (91%)	"Very sure." – Interview 4
		Uncertain initial response	2/22 (9%)	**"**A couple of times a week it will do. I don't know whether you'd call that often or sometimes or – Yeah, probably a couple of nights a week but no more than that." - Interview 9
	Response selection	Consistent response	22/22 (100%)	N/A
		Inconsistent response	0/22 (0%)	N/A

Appendix 13.6. Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Fatigue item

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
Fatigue ("I generally felt tired")	Comprehension	Completely aligned	17/22 (77%)	"Well sometimes it tires you out. If it's aching it does make you tired. So, yeah, I just sit down and rest." – Interview 9
		Partially aligned	2/22 (9%)	"It means like in normal, my everyday life, do I feel tired." – Interview 3
		Completely not aligned	3/22 (14%)	"It means I can't do very much." – Interview 12
	Retrieval	No retrieval difficulty	22/22 (100%)	"But I'm 82. I've also got a thyroid problem. And that can make me tired. So it's a combination thing, I'm afraid." – Female, 82 years old
		Partial Retrieval difficulty	0/22 (0%)	N/A
		Complete Retrieval difficulty	0/22 (0%)	N/A

Appendix 13.6. (*Cont.*) Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Fatigue item.

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
Fatigue ("I generally felt tired")	Judgement	Certain initial response	19/22 (86%)	"I'm 100% sure of that." – Interview 6
		Uncertain initial response	3/22 (14%)	**"Interviewer** So you responded 'often'. **Respondent** Well I suppose it's 'always', isn't it really? When I think about it. It's 'always', isn't it?" - Interview 2
	Response selection	Consistent response	22/22 (100%)	N/A
		Inconsistent response	0/22 (0%)	N/A

Appendix 13.7. Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Original Neuropathic-like pain item.

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
Neuropathic-like pain ('Cold or heat touching my knee was painful')	Comprehension	Completely aligned	5/17 (29%)	"does heat create any pain in the knee?" – Interview 14
		Partially aligned	5/17 (29%)	"It means if, well put heat on it or just water as in the heat, been outside and it's been really cold, it's not really made any difference to it." – Interview 3
		Completely not aligned	7/17 (42%)	"So you know when it's been winter and the cold from the winter makes my leg ache worse!" – Interview 13
	Retrieval	No retrieval difficulty	7/17 (42%)	"Well if I put something too cold on it, it really seizes the knee."– Interview 1
		Partial Retrieval difficulty	6/17 (35%)	"No, I can't say as it does, no" - Reference #1, Interview 16 "Oh no, you know, the odd occasions, you know, i.e., the winter time, yeah. My feet 16 get cold hence my knee gets cold." – Reference #2, Interview 16

Appendix 13.7. (*Cont.*). Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Original Neuropathic-like pain item.

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
Neuropathic-like pain ('Cold or heat touching my knee was painful')	Retrieval	Complete Retrieval difficulty	4/17 (23%)	"I can't say it is really. It's more weight, or hitting it accidentally, or walking into something accidentally."– Female, 82 years old
	Judgement	Certain initial response	11/17 (65%)	"Quite sure."– Interview 18
		Uncertain initial response	6/17 (35%)	"Um, well I'd say I'm unsure." – Interview 18
	Response selection	Consistent response	17/17 (100%)	N/A
		Inconsistent response	0/17 (0%)	N/A

Appendix 13.8. Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Revised Neuropathic-like pain item.

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
Neuropathic-like pain ('Cold or heat e.g. bath water, on my knee was painful')	Comprehension	Completely aligned	5/5 (100%)	"Well if I get in the bath and the water's too hot or it feels cold on my knee and my knee starts playing up - and it doesn't – Interview 18
		Partially aligned	0/5 (0%)	N/A
		Completely not aligned	0/5 (0%)	N/A
	Retrieval	No retrieval difficulty	3/5 (60%)	"Um, yeah sometimes when I am in the bath- And it's bad, like a toothache pain but not really a bearable one, like." – Interview 21
		Partial Retrieval difficulty	2/5 (40%)	"Just really uncomfortable at times, it depends on how much pain you're in at the time 28 anyway, because I think hot water sometimes will ease it but it doesn't at times." – Interview 19
		Complete Retrieval difficulty	0/5 (0%)	N/A

Appendix 13.8. (*Cont*.). Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Revised Neuropathic-like pain item.

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
Neuropathic-like pain ('Cold or heat e.g. bath water, on my knee was painful')	Judgement	Certain initial response	4/5 (80%)	"Quite sure." – Interview 18
		Uncertain initial response	1/5 (20%)	**Interviewer** Has that happened at any point in the last week? **Respondent** No - Reference #1, Interview 19 **Interviewer** So you said 'sometimes' to the question - **Respondent** Yeah. **Interviewer** No. So how sure are you of that answer? **Respondent** I'm positive. - Reference #2, Interview 19
	Response selection	Consistent response	5/5 (100%)	N/A
		Inconsistent response	0/5 (0%)	N/A

Appendix 13.9. Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Pain Distribution item

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
Pain Distribution ("The final question is about 'pain that 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. And by pain, we mean aching and discomfort, but we don't mean pain due to feverish illnesses such as flu.")	Comprehension	Completely aligned	14/22 (64%)	"Shade in the parts where you ache most each day." – Interview 19
		Partially aligned	8/22 (36%)	"To tell me where my pain is." – Reference #1, Interview 15 "And how bad it is." – Reference #2, Interview 15
		Completely not aligned	0/22 (0%)	N/A
	Retrieval	No retrieval difficulty	19/22 (86%)	"Because that's where it [pain] mainly is. It's round here, you know, it's not at the back of my knee, it's the front, it's when I bend the knees, it feels like the sockets either go together or they're going to come apart, that's what it feels like." – Interview 15
		Partial Retrieval difficulty	3/22 (14%)	**Interviewer** Is that the only place you feel pain? **Respondent** It does from that stiffness in the knee but I do get round my ankles for the bad circulation. – Interview 9

Appendix 13.9 (*Cont.*). Table showing proportion of participants providing responses respective to each study code and sub-code based on Tourangeau's question response model – Pain Distribution item.

Trait (Item)	Category	Sub category	Participants (%)	Units of meaning
Pain Distribution ("The final question is about 'pain that 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. And by pain, we mean aching and discomfort, but we don't mean pain due to feverish illnesses such as flu.")	Retrieval	Complete Retrieval difficulty	0/22 (0%)	N/A
	Judgement	Certain initial response	22/22 (100%)	"Oh pretty sure. Yeah, really sure." – Interview 4
		Uncertain initial response	0/22 (0%)	N/A
	Response selection	Consistent response	22/22 (100%)	N/A
		Inconsistent response	0/22 (0%)	N/A

Appendix 13.10. Table showing number of participants with problems indicative of poor item function for each item

Items	Number of individuals with problems			
	1 problem	2 problems	3 problems	Total
Neuropathic-like pain ('Cold or heat touching my knee was painful')*	5	3	1	10
Fatigue ("I generally felt tired")	5	0	0	5
Cognitive impact ("Knee pain stopped me concentrating on what I was doing")	2	5	0	7
Catastrophizing ("I kept thinking about how much my knee hurts")	1	0	0	0
Anxiety ("In general, I got sudden feelings of panic")	0	0	0	0
Sleep ("Knee pain affected my sleep")	1	0	0	1
Depression ("I generally still enjoyed the things I used to enjoy")	3	0	0	2
Pain Distribution ("The final question is about 'pain that 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. And by pain, we mean aching and discomfort, but we don't mean pain due to feverish illnesses such as flu.")	0	0	0	0
All items	8	7	1	16

Appendix 13.11. Final version of the CAP-Knee questionnaire.

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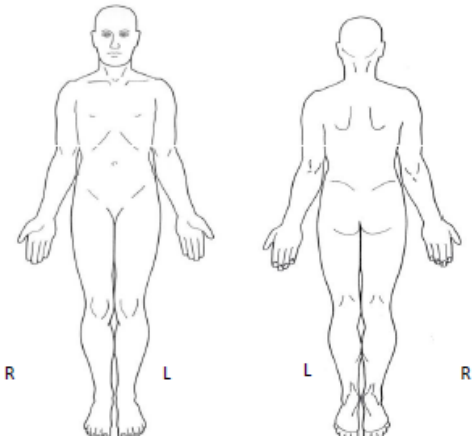
CAP-Knee (Central Aspects of Pain in the Knee) Questionnaire

Name: _____ Date: _____

Please select the response that best describes how you have felt **over the PAST *WEEK*.**
Please tick one box only per statement and try not to leave any statements blank.

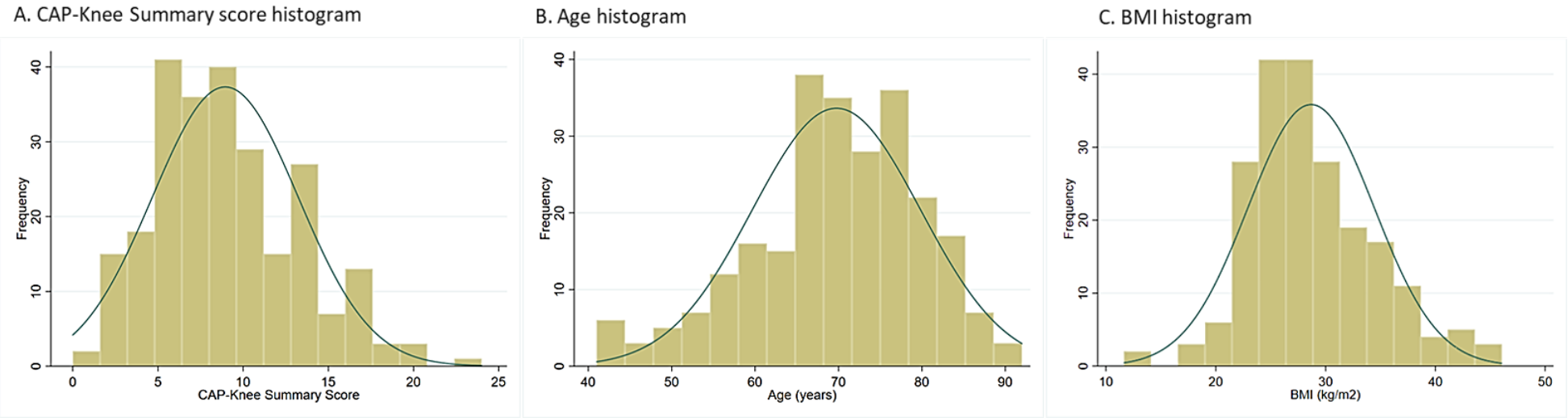
		Never	Sometimes	Often	Always
1.	Cold or heat (e.g. bath water) on my knee was painful	☐	☐	☐	☐
2.	I generally felt tired	☐	☐	☐	☐
3.	Knee pain stopped me concentrating on what I was doing	☐	☐	☐	☐
4.	I kept thinking about how much my knee hurts	☐	☐	☐	☐
5.	In general, I got sudden feelings of panic	☐	☐	☐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

8. This final 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.



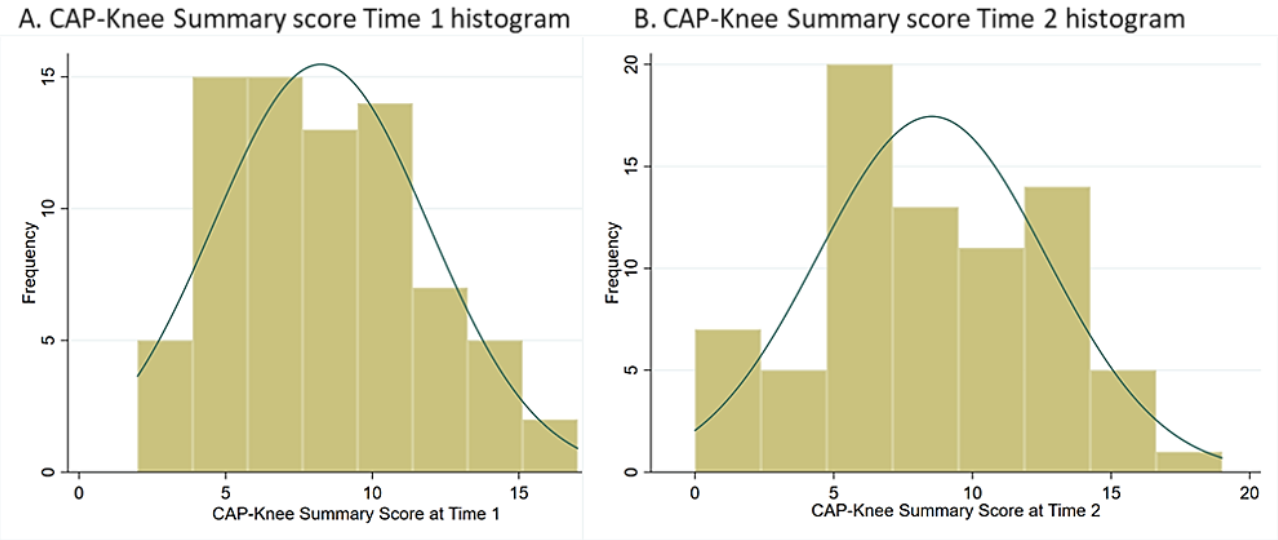
Appendix 14. Figures showing histograms for CAP-Knee study measures within baseline study (n=250) - and repeatability sub study-(76) populations.

Appendix 14.1. Figure showing histograms for CAP-Knee summary scores, Age and BMI within baseline population (n=250).



Histograms for **A.** CAP-Knee summary score (skewedness=0.49; kurtosis = 3.54; Shapiro Wilk's p-value = 0.00008); **B.** Age (skewedness=-0.55; kurtosis = 3.15; Shapiro Wilk's p-value = 0.0005) and **C.** BMI (skewedness=0.49; kurtosis = 3.45; Shapiro Wilk's p-value = 0.0003) suggest that these baseline data (n=250) are skewed.

Appendix 14.2. Figure showing histograms for CAP-Knee summary scores within repeatability population (n=76).



Histograms for **A.** CAP-Knee summary score at Time 1 (skewedness=0.31; kurtosis = 2.37; Shapiro Wilk's p-value = 0.27); and **B.** CAP-Knee summary score at Time 2 (skewedness=0.04; kurtosis = 2.50; Shapiro Wilk's p-value = 0.96) suggest that these baseline data (n=250) are normally distributed.

Appendix 15. Supplementary findings supporting CAP-Knee psychometric validation chapter

Appendix 15.1. Table showing fit statistics for item response categories included within the 8-item partial credit model.

Items	Response Categories (n, %)	Difficulty logit	SE logit	Outfit MNSQ	Infit MNSQ
Neuropathic- like pain[#]	1 (10%)	1.09	0.15	0.99	1.00
	2 (8%)	1.77	0.23	1.34	1.04
	3 (3%)	2.12	0.39	1.89	1.05
Fatigue[#]	1 (45%)	-2.23	0.23	1.79	1.04
	2 (28%)	0.47	0.15	1.04	1.03
	3 (18%)	1.04	0.19	1.62	1.11
Cognitive impact[#]	1 (45%)	-0.44	0.15	0.78	0.88
	2 (16%)	1.45	0.18	0.57	0.79
	3 (3%)	2.81	0.41	0.64	0.92

Table continued on next page.
MNSQ = Mean Squares; SE = Standard Error; 'Never' was responded to by 66% of participants for the NP-Like symptoms item; 10% for the Fatigue item; 36% for the Cognitive impact item.
*Item showing disordering of the step difficulty; [#]Item with response categories showing misfitting outfit MNSQ values

Appendix 15.1. (*Cont.*). Table showing fit statistics for item response categories included within the 8-item partial credit model.

Items	Response Categories (n, %)	Difficulty logit	SE logit	Outfit MNSQ	Infit MNSQ
Catastrophizing	1 (52%)	-1.23	0.17	0.75	0.93
	2 (16%)	1.40	0.17	0.82	0.93
	3 (9%)	1.48	0.25	0.72	0.93
Anxiety[#]	1 (21%)	1.34	0.16	0.96	0.97
	2 (6%)	2.09	0.27	1.78	1.17
	3 (2%)	2.65	0.54	0.37	1.00
Sleep disturbance*	1 (44%)	-0.61	0.15	0.83	0.91
	2 (14%)	1.47	0.17	0.78	0.92
	3 (10%)	1.19	0.24	1.26	0.98

Table continued on next page.
MNSQ = Mean Squares; SE = Standard Error; 'Never' was responded to by 22% for the Catastrophizing item; 72% for the Anxiety item; 32% for the Sleep disturbance item; 24% for the Depression item; and 27% for the Pain Distribution item.*Item showing disordering of the step difficulty; [#]Item with response categories showing misfitting outfit MNSQ values

Appendix 15.1. (*Cont.*). Table showing fit statistics for item response categories included within the 8-item partial credit model.

Items	Response Categories (n, %)	Difficulty logit	SE logit	Outfit MNSQ	Infit MNSQ
Depression[#]	1 (28%)	-0.67	0.17	1.35	1.09
	2 (32%)	-0.07	0.15	1.05	1.05
	3 (1%)	1.35	0.19	2.68	1.13
Pain distribution[#]	1 (73%)	-1.19	0.15	1.23	1.15

MNSQ = Mean Squares; SE = Standard Error; 'Never' was responded to by 66% of participants for the NP-Like symptoms item; 10% for the Fatigue item; 36% for the Cognitive impact item; 22% for the Catastrophizing item; 72% for the Anxiety item; 32% for the Sleep disturbance item; 24% for the Depression item; and 27% for the Pain Distribution item.*Item showing disordering of the step difficulty; [#]Item with response categories showing misfitting outfit MNSQ values

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Appendix 15.2. Table showing fit statistics for item response categories included within the 8-item partial credit model, with all items rescored

Items	Response Categories (n, %)	Difficulty logit	SE logit	Outfit MNSQ	Infit MNSQ
Neuropathic- like pain[#]	1 (23%)	1.12	0.16	1.02	1.02
	2 (11%)	1.70	0.23	1.49	1.06
Fatigue[#]	1 (45%)	-2.63	0.24	1.99	1.07
	2 (45%)	0.11	0.14	1.03	1.01
Cognitive impact[$]	1 (45%)	-0.50	0.15	0.72	0.85
	2 (19%)	1.46	0.18	0.62	0.83
Catastrophizing	1 (52%)	-1.33	0.17	0.72	0.93
	2 (25%)	1.14	0.17	0.83	0.93

MNSQ = Mean Squares; SE = Standard Error
[$]Items excluded from the model. [#]Item with response categories showing misfitting outfit MNSQ values.
'Never' was responded to by 66% of participants for the NP-Like symptoms item; 10% for the Fatigue item; 22% for the Catastrophizing item; 72% for the Anxiety item; 32% for the Sleep disturbance item; and 24% for the Depression item.

Appendix 15.2. (*Cont*.). Table showing fit statistics for item response categories included within the 8-item partial credit model, with all items rescored.

Anxiety[#]	**1 (21%)**	**1.39**	**0.16**	**0.99**	**0.99**
	2 (7%)	2.14	0.27	2.40	1.17
Sleep disturbance	1 (44%)	-0.67	0.16	0.81	0.91
	2 (24%)	1.12	0.17	0.75	0.89
Depression	1 (28%)	-0.78	0.17	1.40	1.15
	2 (48%)	-0.34	0.15	1.12	1.07
Pain distribution[$]	1 (73%)	-1.26	0.16	1.39	1.20

MNSQ = Mean Squares; SE = Standard Error
[$]Items excluded from the model. [#]Item with response categories showing misfitting outfit MNSQ values.
'Never' was responded to by 66% of participants for the NP-Like symptoms item; 10% for the Fatigue item; 22% for the Catastrophizing item; 72% for the Anxiety item; 32% for the Sleep disturbance item; and 24% for the Depression item.

Appendix 15.3. Table showing fit statistics for item response categories included within the 6-item partial credit model, with all items rescored.

Items	Response Categories (%)	Difficulty logit	SE logit	Outfit MNSQ	Infit MNSQ
Neuropathic- like pain[#]	1 (23%)	1.13	0.16	1.00	0.99
	2 (11%)	1.65	0.23	1.66	1.05
Fatigue[#]	1 (45%)	-2.35	0.24	1.51	1.07
	2 (45%)	0.12	0.14	0.99	0.99
Cognitive impact[$]	-	-	-	-	-
Catastrophizing	1 (52%)	-1.30	0.17	0.79	0.96
	2 (25%)	1.13	0.16	0.92	0.98
Anxiety[#]	1 (21%)	1.39	0.16	0.99	0.99
	2 (7%)	2.08	0.27	1.58	1.17

Table continued on next page
MNSQ = Mean Squares; SE = Standard Error
[$]Items excluded from the model. [#]Item with response categories showing misfitting outfit MNSQ values.
'Never' was responded to by 66% of participants for the NP-Like symptoms item; 10% for the Fatigue item; 22% for the Catastrophizing item; 72% for the Anxiety item;.

Appendix 15.3. (Cont.) Table showing fit statistics for item response categories included within the 6-item partial credit model, with all items rescored.

Sleep disturbance[#]	**1 (44%)**	**-0.65**	**0.16**	**0.85**	**0.93**
	2 (24%)	1.11	0.17	0.79	0.92
Depression	1 (28%)	-0.75	0.17	1.23	1.11
	2 (48%)	-0.33	0.15	1.07	1.02
Pain distribution[$]	-	-	-	-	-

MNSQ = Mean Squares; SE = Standard Error
[$]Items excluded from the model. [#]Item with response categories showing misfitting outfit MNSQ values.
'Never' was responded to by; 32% of participants for the Sleep disturbance item; and 24% for the Depression item

Appendix 15.4. Table showing inter item correlation for true population item scores.

	Neuropathic-like symptoms	Fatigue	Cognitive impact	Catastrophizing	Anxiety	Sleep disturbance	Depression
Fatigue	0.24***	1.00					
Cognitive impact	0.37***	0.28***	1.00				
Catastrophizing	0.34***	0.22***	0.66***	1.00			
Anxiety	0.24***	0.27***	0.39***	0.25***	1.00		
Sleep disturbance	0.37***	0.29***	0.59***	0.53***	0.31***	1.00	
Depression	0.21**	0.31***	0.33***	0.27***	0.27***	0.28***	1.00
Pain Distribution	0.08	0.16*	0.07	0.04	0.12	0.14*	-0.01

*p<0.05; **<p<0.01; ***p<0.001

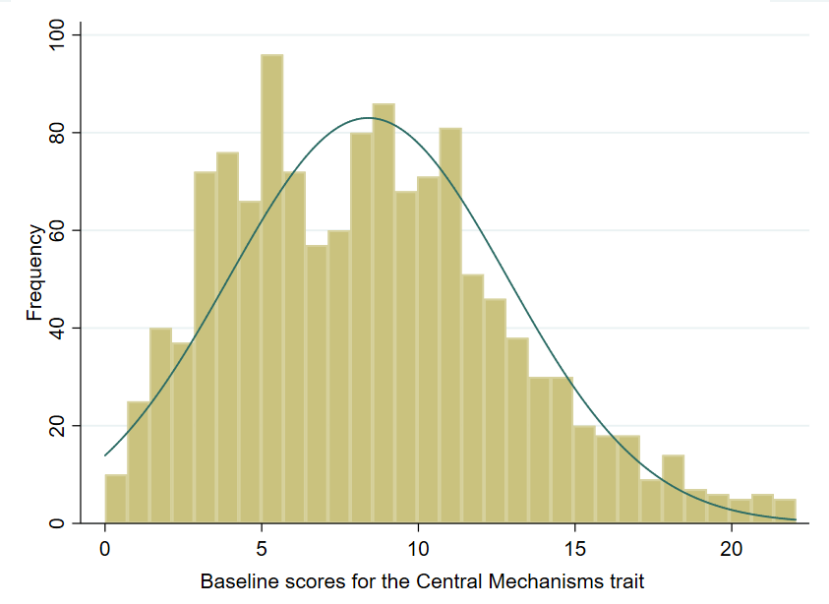
Appendix 15.5. Table showing inter item correlation for Rasch transformed item scores

	Neuropathic-like symptoms	Fatigue	Cognitive impact	Catastrophizing	Anxiety	Sleep disturbance	Depression
Fatigue	0.26***	1.00					
Cognitive impact	0.37***	0.27***	1.00				
Catastrophizing	0.33***	0.22***	0.66***	1.00			
Anxiety	0.24***	0.27***	0.38***	0.24***	1.00		
Sleep disturbance	0.36***	0.31***	0.59***	0.52***	0.31***	1.00	
Depression	0.22***	0.30***	0.33***	0.26***	0.29***	0.32***	1.00
Pain Distribution	0.08	0.14*	0.07	0.04	0.12	0.13*	-0.01

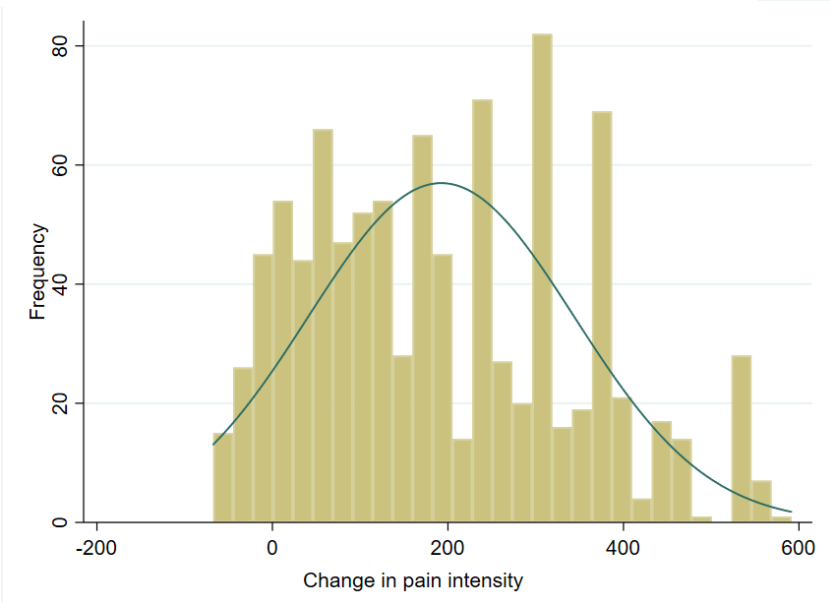
*p<0.05; **<p<0.01; ***p<0.001

Appendix 16. Histograms for the ‘Central Mechanisms trait’ and the ‘residualized change in pain intensity scores’ within the KPIC study.

A. Histogram for baseline Central Mechanisms trait scores



B. Histogram for residualized change in pain intensity scores



Histograms for **A**. Baseline scores for the Central Mechanisms trait (skewedness=0.49; kurtosis = 2.84; Shapiro Wilk’s p-value < 0.00001); and **B.** Residualized change in pain intensity (skewedness=0.41; kurtosis = 2.34; Shapiro Wilk’s p-value < 0.00001). These suggest that these variables were normally distributed.