

BMJ Open

Pain sensitization and the risk of poor outcome following physiotherapy for knee osteoarthritis: protocol for a prospective cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-007430
Article Type:	Protocol
Date Submitted by the Author:	11-Dec-2014
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Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Pain management < ANAESTHETICS

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7 knee osteoarthritis: protocol for a prospective cohort study
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38 Keywords: knee osteoarthritis, pain, central nervous system sensitization,
39 physiotherapy
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41 Word count: 4070
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ABSTRACT

Introduction

Pain is the dominant symptom of knee osteoarthritis and recent evidence suggests factors outside of local joint pathology, such as pain sensitization, can contribute significantly to the pain experience. It is unknown how pain sensitization influences outcomes from commonly employed interventions such as physiotherapy.

The aims of this study are, firstly to identify people with knee osteoarthritis who display signs and symptoms associated with pain sensitization using clinical tools and quantitative sensory testing. Secondly, we will investigate if indications of pain sensitization at baseline are associated with poor outcome following physiotherapy.

Methods and analysis

This is a multi-centre prospective cohort study with 140 participants. Eligible patients with moderate/severe symptomatic knee osteoarthritis will be identified at outpatient clinics. A baseline assessment will provide a comprehensive description of the somatosensory characteristics of each participant; by means of clinical examination, quantitative sensory testing and validated questionnaires measuring pain and functional capacity. Participants will then undergo physiotherapy treatment. The primary end point will be on completion of physiotherapy (estimated to be at 3 months) and questionnaires will assess change in pain, disability (sub-scales of Western Ontario and McMaster University Score Osteoarthritis Index) and participants' global rating of change. These primary outcome measures will dichotomise participants into treatment 'responders' and 'non-responders' according to the Osteoarthritis Research Society International (OARSI) treatment responder criteria.

For data analysis results from pressure pain thresholds, temporal summation and conditioned pain modulation will create a composite score of pain sensitization. Logistic regression will explore the relationship between response to physiotherapy and pain sensitization while accounting for confounders.

Ethics and dissemination

This study has been approved by St. James's Hospital/AMNCH Research Ethics Committee and by the St. Vincent's Healthcare Group Ethics and Medical Research

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3 Committee. The results will be presented at international conferences and published
4 in a peer review journal.
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7 **Trial Registration Number** ClinicalTrials.gov Identifier: NCT02310945
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10 11 **ARTICLE SUMMARY** 12

13 14 **Strengths and limitations of this study** 15

16 To our knowledge this is the first study examining the effects of pain sensitization on
17 physiotherapy outcomes in knee osteoarthritis.
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20 Strengths of this study protocol include; the relatively large sample given the
21 comprehensive assessment procedure involved, the use of a broad range of
22 validated measures to study pain processing and the gathering of control QST data
23 from healthy volunteers.
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27 This study will focus on tests to identify features of pain sensitivity based on their
28 utility and practicality in the clinical setting. However these criteria necessitate the
29 exclusion of certain tests, such as thermal pain thresholds, that are difficult to
30 carrying out reliably in the clinical setting in a limited assessment time.
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34 As this is a clinically based observational study there is likely to be variation in
35 physiotherapy intervention. The findings of this research may call for a further
36 research examining the effects of a targeted treatment programme for pain
37 sensitization compared to usual care.
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INTRODUCTION

Knee osteoarthritis (OA) is a prevalent joint disease that causes a huge burden of pain, disability and loss of productivity worldwide.[1–3] With ageing populations and increasing obesity, the prevalence of OA is rising, thus its timely and effective management is a priority within healthcare.[3,4]

The pathophysiology of knee OA pain is complex. Altered processing of nociceptive inputs at spinal and higher brain centers may help explain discrepancies between pain severity and pathological abnormalities in OA.[5–7] Pain sensitization is defined as increased responsiveness of nociceptive neurons to their normal input and/or recruitment of a response to normally sub-threshold inputs.[8] It is proposed that these changes in central pain processing due to chronic nociceptive input into the nervous system from the arthritic can contribute to an enhanced, persistent and more widespread pain response.[9,10] Recent studies in knee OA have found the presence of increased pain sensitivity at remote sites, enhanced temporal summation (TS) and hypersensitivity to various stimuli to be associated with reports of more severe symptoms.[5,6,11] These cross-sectional studies linking features of sensitization to greater levels of pain and disability do not explore if pain sensitivity has any prognostic implications.

There is some evidence to suggest increased pain sensitivity negatively affects treatment outcomes. In painful musculoskeletal conditions such as shoulder impingement and lateral epicondylalgia widespread pressure pain sensitivity and thermal hyperalgesia, have been linked with a poorer prognosis.[12,13] Surgical outcomes for knee osteoarthritis may also be affected with the presence of increased pain sensitivity prior to total knee replacement associated with more persistent pain after surgery.[14,15]

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3 Although joint replacement is considered an effective treatment for end-stage knee
4 OA, the majority of patients with knee OA are managed conservatively.
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6 Physiotherapy is a widely recommended conservative treatment approach.[16]
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8 Studies of prognosis in knee OA have focused on demographic and psychological
9 variables[17–19], few studies have focused on factors relating to abnormal pain
10 processing. Despite recent claims that the domain of altered central pain processing
11 makes an important contribution to the clinical pain experience in some people with
12 knee OA[20], no longitudinal studies have explored prognostic factors relating to pain
13 sensitization and outcome following physiotherapy. In whiplash associated disorders
14 the presence of sensory hypersensitivity and cold hyperalgesia has been shown to
15 reduce the likelihood of a positive response to physiotherapy treatment.[21] Thus it is
16 conceivable, but currently unproven, that knee OA patients with evidence of pain
17 sensitization have poorer outcomes following physiotherapy.
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24 One obstacle to investigating the implications of pain sensitization is reliably
25 identifying it in the clinical setting. Clinical criteria proposed for assessing central
26 sensitization rely principally on the clinician's subjective interpretation of patient
27 symptoms.[22] Although useful clinically, for research purposes more objective
28 measures are preferable. Due to the complexity of the pain experience it is
29 inadvisable to rely on any single test to reflect peripheral and central pain
30 mechanisms.[23,24] A multi-tissue assessment using a multi-modal stimuli approach
31 has been advocated,[25], and will be adopted in this study. Recognised features of
32 central and peripheral sensitization previously identified in knee OA patients will be
33 utilised in this study and these include extended areas of hyperalgesia,[26,27],
34 enhanced TS,[6,9], and dysfunctional conditioned pain modulation (CPM).[9,27]
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41 This study will explore clinical outcomes of knee OA (pain, function, patient's global
42 assessment) following physiotherapy, investigating the association between key
43 features of pain sensitization and the likelihood of a poor outcome. Distinguishing
44 patients at risk of a poor outcome may help determine appropriate management
45 strategies in a timely manner.
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49 **Study aims**

50 The main aims of the study are; firstly to provide a comprehensive description of the
51 somatosensory characteristics of people with pain associated with knee OA (by
52 means of quantitative sensory testing (QST), and validated questionnaires
53 measuring pain, functional capacity and quality of life) and secondly, to investigate if
54 the presence of pain sensitization at baseline is associated with poorer response to
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3 physiotherapy treatment. We hypothesise that the presence of pain sensitization at
4 baseline is associated with a greater risk of poor outcome at a follow-up post
5 physiotherapy treatment
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9 **METHODS AND ANALYSIS**

11 **Study design**

12 A multi-centre observational cohort study with assessments at baseline, post-
13 treatment and at six months will be conducted. Following the baseline assessment
14 for features of pain sensitization all participants will receive usual physiotherapy care.
15 The relationship between pain sensitization and outcomes in terms of pain and
16 disability will be explored through regression analysis.
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23 **Setting**

24 The study will be set in the physiotherapy outpatient departments of three large
25 publicly funded teaching hospitals in Dublin, Ireland.
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29 **Participants**

30 Patients with symptomatic knee OA referred for physiotherapy treatment by a
31 hospital consultant or clinical specialist physiotherapist will be eligible for inclusion.
32 Full details of inclusion/exclusion criteria are summarised in Table 1.
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36 At the time of recruitment knee pain must be the participant's primary
37 musculoskeletal complaint they are seeking treatment for, and physiotherapy must
38 be the main treatment being undertaken over the study period. Participants recruited
39 at musculoskeletal assessment clinics will be screened by the clinical specialist
40 physiotherapist. Patients on the physiotherapy waiting list will be screened for
41 suitability by the principal investigator over the telephone.
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46 Table 1. Study inclusion and exclusion criteria
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Inclusion Criteria	
Diagnosis	Knee osteoarthritis diagnosed by American College of Rheumatology clinical criteria
Age	Over 50 years
Pain duration	Knee pain for at least 6 months
Severity	Pain \geq 5/10 on Numerical Rating Scale

Medication	Willing to abstain from simple analgesics and NSAIDs for 24 hours prior to testing
Consent	Willing and able to give full consent
Exclusion Criteria	
Pathology	Lumbar or cervical radiculopathy, systematic inflammatory disease, positive screen for diabetic neuropathy, neuropathic pain
Past medical history	Previous surgery or disease of the peripheral or central nervous system, sensory loss secondary to chemotherapy or radiotherapy, fibromyalgia, chronic fatigue syndrome
Cognitive ability	Cognitive or psychiatric disorder interfering with ability to fully consent or cooperate with assessment
Other treatment	Injection or physiotherapy treatment for knee joint within previous 3 months
Medication	Taking anti-depressant or anti-convulsant medication

Healthy controls

Healthy participants are defined as people with no current pain or chronic pain problems in the past year. Forty age and gender matched controls will be recruited from the general population, and from the staff and student population in University College Dublin. The controls will provide reference data for QST results and enable calculation of standardised z scores using the following formula: $z = (\text{value}_{\text{participant}} - \text{mean}_{\text{controls}}) / \text{standard deviation}_{\text{controls}}$. This allows comparison of QST results between controls and knee pain participants independent of the unit of measurement.[28]

Investigator

The principal investigator will be a senior physiotherapist with twelve years clinical experience. The same investigator will carryout all tests and is trained in using QST.

Recruitment procedure

A consecutive sample of knee osteoarthritis patients with moderate/severe knee pain will be recruited. Between June 2014 and July 2015 potentially eligible participants will be identified at musculoskeletal assessment clinics and from physiotherapy outpatient waiting lists. A feasible recruitment rate is estimated at 12 patients per month with recruitment continuing until the specified numbers are achieved. Those who agree to participate will attend for a baseline assessment prior to commencing physiotherapy treatment. Written informed consent will be obtained before enrolment in the study. Figure 1 represents the flow of participants through the study.

Physiotherapy management

Physiotherapy treatment will be in line with current clinical guidelines for the management of knee OA.[29] Treatment will typically involve between four and six physiotherapy appointments. In some cases treatment may take the format of a small group exercise intervention. A workshop led by the principal investigator will be held at each recruitment site prior to study commencement where physiotherapists will receive an update on clinical guidelines and current best evidence on management of knee OA. This will standardise treatment to some degree, but intervention will be individualised at the discretion of the treating physiotherapist and in consultation with the patient.

At each appointment the treating physiotherapist will record by means of a checklist the type and duration of treatment, patient adherence and any treatment side effects.

Assessment

Baseline assessment

A schematic view of the outcome measures recorded at baseline and follow up is presented in Table 2. Each baseline assessment will take approximately 50 minutes to complete at the physiotherapy clinic by the principal investigator. Some questionnaires will be posted and completed in advance by participants.

Follow up assessment

The primary endpoint will be at completion of physiotherapy treatment, this time point is estimated to be on average at 3 months. Physiotherapy administration staff will alert the principal investigator when a participant is discharged. Thereupon pain, disability and global rating of change will be assessed by means of a postal questionnaire. Information will also be recorded on use of co-interventions or change in medication for knee pain.

Six months after enrolment into the study participants will complete a postal questionnaire assessing pain and function. They will exit the study at this point.

Assessment procedures and minimising bias

In order to improve reliability of the assessment and minimise bias standardised assessment procedures will be followed. Studies support the reliability of QST measures where protocols are standardised and both the tester and participant are carefully instructed.[25] At each location testing will be undertaken in the same temperature controlled room by the same investigator, using a single set of testing

devices. Each session will begin by familiarising participants with standardised test procedures.[30,31] Physical testing will be performed prior to in-depth subjective assessment or without knowledge of questionnaire scores. Test order is important,[32], and a pre-determined sequence will be used beginning with non-noxious stimuli. CPM can induce a residual effect and will be the final test.[33] With bilateral symptoms the most painful knee will be selected, if both are equally symptomatic the right knee will be tested.

Table 2. Outcome measures and collection points

Domain	Variable	Instrument for Data Collection	Collection Points
Demographics	Age, Gender, Educational attainment, Employment status, Martial status	Baseline assessment questionnaire	Baseline
Pain	Self reported pain	WOMAC pain sub-scale	Baseline, post treatment*, 6 months
	Pain intensity	Numerical rating scale	Baseline, 6 months
	Location & quality	Knee Pain Map	Baseline
	Neuropathic pain symptoms	Modified PainDETECT	Baseline
	Characteristics of osteoarthritic pain	Intermittent and Constant Osteoarthritis Pain Instrument	Baseline
	Widespread pain	Body chart Manual tender point count	Baseline
Function	Self reported function	WOMAC function sub-scale	Baseline, post treatment, 6 months
Quality of life	Health related quality of life	EQ-5D 5L	Baseline
Central Sensitization Symptoms	Non-musculoskeletal central sensitization symptoms	Central Sensitization Inventory	Baseline
Quantitative Sensory Testing	Light touch	Von Frey filaments	Baseline
	Vibration	Graded tuning fork	Baseline
	Pain pressure Thresholds	Pressure algometry	Baseline
	Dynamic allodynia	Brush stroke	Baseline
	Static allodynia	Von Frey Filaments	
	Thermal hyperalgesia	Thermo-rollers	Baseline
	Temporal summation	Repetitive mechanical stimuli with weighted pinprick	Baseline

	Conditioned pain modulation	Cold pressor test	Baseline
Confounding Variables	Obesity	Ratio of waist circumference to height	Baseline
	Depressive symptoms	Centre for Epidemiologic Studies Depression Scale	Baseline
	Comorbidities	Self Administered Comorbidity Questionnaire	Baseline
Management related variables	Treatment adherence	Sports Injury Rehabilitation Adherence Scale	During treatment
		Patient attendance ratio	During treatment
		Home Exercise Compliance Assessment	During treatment
	Treatment type and duration, Adverse effects	Therapist record sheet	During treatment
	Medication use and co-interventions	Follow-up questionnaire	Post treatment, 6 months
Treatment outcome	Response to treatment	OARSI Responder Criteria; WOMAC pain and function subscales, global rating of change	Post treatment

* Post treatment assessment will be at approximately 3 months

Primary outcome measure

The main outcome is a positive response to physiotherapy treatment and this will be determined using a set of responder criteria by the Outcome Measures in Rheumatology - Osteoarthritis Research Society International (OMERACT-OARSI).[34] The criteria will be applied to the relevant data gathered at post treatment follow-up and identify 'responders' and 'non-responders' to physiotherapy. The responder criteria are summarised in Figure 2. For application of the criteria pain and function will be measured with the subscales of the Western Ontario and McMaster's University Score Osteoarthritis Index (WOMAC LK 3.0). Validity and reliability of these subscales are well established, including for postal surveys.[35–37] Global rating of change will be measured with a 7-point Likert scale. This scale captures relevant change by asking the patient about any improvement or deterioration that has occurred with physiotherapy treatment.[38] Two points on the scale will represent a 20% improvement.

Secondary outcome measures

Pain assessment

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3 The following valid and reliable measures of pain will be recorded; The Pain Intensity
4 Numerical Rating Scale (Pain NRS) will measure participant's average pain intensity
5 over the previous seven days.[39,40] The Knee Pain Map will be used to record
6 more detailed information about the location and quality of knee pain.[41]
7
8 Widespread pain is defined for this study according to the American College of
9 Rheumatology classification criteria using pain drawings marked by participants on a
10 body manikin.[42] Widespread pain is associated with more severe knee pain and
11 functional decline.[43,44]
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16 **Pain and quality of life questionnaires**

17 *Modified PainDETECT (mPD-Q)*

18 This questionnaire will record any neuropathic component to participants' symptoms.
19 It has been previously used for the screening of neuropathic pain-like symptoms in
20 knee OA in an elderly cohort.[45] Participants with more neuropathic pain-like
21 symptoms (scores > 12/38) are more likely to have signs of central sensitisation.[46]
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27 *Intermittent and Constant Osteoarthritis Pain Instrument (ICOAP)*

28 This validated questionnaire assesses various facets of both intermittent and
29 constant pain for the knee, including effects on sleep and quality of life, degree of
30 frustration and worry associated with the pain.[47] Two predictability items will be
31 administered to capture unpredictable spontaneous pain, thought to have the
32 greatest impact on participant well-being.[48]
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38 *Central Sensitization Inventory (CSI)*

39 This self-report inventory has preliminary validity and reliability and assesses for
40 symptoms not related to the musculoskeletal system but common to central
41 sensitization syndromes.[49,50] Good sensitivity (81%) and specificity (79%) values
42 were found with a cut-off score of 40 (out of 100) to identify patients with symptoms
43 of central sensitization.[50]
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48 *EuroQoL EQ-5D*

49 The EQ-5D is a frequently used generic quality of life instrument, designed by the
50 EuroQoL group.[51] A modified form has been developed with an enlarged number
51 of possible answers to avoid a ceiling effect.[52] The EQ-5D has acceptable reliability
52 and validity when used in patients with knee OA.[53]
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58 **Quantitative Sensory Testing (QST)**

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3 QST is a psychophysiological measure of perception in response to external stimuli
4 of controlled intensity.[31] This QST protocol will make reference to the well-
5 established German Neuropathic Pain Consortium (DFNS) protocol,[31], and will
6 utilise clinical QST methods recommended by the International Association for the
7 Study of Pain.[30] This current study's assessment protocol aims to be more
8 accessible using tools that are relatively inexpensive and adaptable to the clinical
9 setting.[54]

10
11 Test sites used will be as follows; *Site 1*: On the medial or lateral knee joint line,
12 depending where the patient indicates their greatest pain (3 cm medial to medial
13 edge of patella or corresponding site laterally), *Site 2*: Over ipsilateral tibialis anterior
14 muscle (5 cm distal to the tibial tuberosity), *Site 3*: On the contralateral forearm (5 cm
15 distal to lateral epicondyle of humerus on the volar aspect). Somatosensory
16 abnormalities over the area of *Site 2* tibialis anterior are thought to provide evidence
17 of spreading sensitisation from the symptomatic knee. Changes at *Site 3* would
18 indicate more widespread sensitisation at a generalised level in the central nervous
19 system.[9]

27 28 *Light touch*

29 Mechanical detection thresholds will be tested using a set of von Frey filaments
30 (Opti-hair2-Set, Marstock, Germany). Monofilaments beginning with the smallest
31 diameter will be applied to the skin. Light touch threshold (gm/mm^2) will be recorded
32 as the last filament (gm/mm^2) that can be perceived. Test-retest reliability of this
33 method for knee OA has been established.[28]

37 38 *Mechanical allodynia*

39 Dynamic mechanical allodynia will be assessed by lightly stroking the knee and
40 forearm with a brush stroke three times (Senselab Brush No 5, Somedic). Static
41 allodynia will be assessed using von Frey filaments. The presence of mechanical
42 allodynia will be recorded if this non-noxious stimulation evokes a sensation of
43 pain.[55]

47 48 *Thermal hyperalgesia*

49 Thermal rollers with predetermined temperatures of 25°C (cold) and 40°C (warm)
50 (Senselab Rolltemp Somedic) will be used to detect thermal hyperalgesia at the
51 forearm and knee.[54] Participants will be asked to report if the thermal sensation is
52 perceived as painful when the rollers are passed lightly over the skin.
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Vibration

Vibration detection threshold will be measured with a graded tuning fork (Rydel–Seiffer, 64 Hz) placed over 3 bony prominences (ulnar styloid, patella and medial malleolus). Vibration detection threshold is determined as a mean disappearance threshold of the vibrations on an 8/8 scale with the stimulus repeated three times.[31]

Pressure pain thresholds (PPTs)

Pressure will be applied using an electronic digital algometer with a probe size of 1 cm² (SomedicAB, Sweden) and an application rate of 30 kPa/s. The participant will be instructed to press an automatic cut off button when the first sensation of pressure pain is perceived. A cut-off point is set at 1000kPa. PPTs will be measured 3 times at the 3 test sites; the first measurement will be excluded and the mean of the last two measurements will be used for analysis. Test-retest reliability using this technique has been demonstrated in patients with knee OA.[56]

Mechanical temporal summation (TS)

The participant will assign a pain rating to a single stimulus by a weighted pinprick (MRC Systems 256 mN) and for a series of 10 pinprick stimuli of the same intensity (1/s applied within an area of 1 cm²).[57] This procedure will be applied twice on a marked area the forearm and knee site. The mean pain rating of the pinprick trains minus the mean pain rating of the single stimuli will give a value for TS.[58,59]

Conditioned pain modulation (CPM)

The cold presser test is recommended for assessment of CPM in the clinical setting. [60,61] The test stimulus will be PPT; the conditioning stimulus will be cold immersion. PPTs will be recorded as outlined above. With the participant seated comfortably, the opposite arm to that used for PPT testing will be immersed in a bath of icy water (4°C monitored by thermometer) up to the elbow for 60 seconds. Participants unable to tolerate the water bath will rate their pain before withdrawing the arm (aim for at least 5 on NRS).[33] Re-testing of PPTs on the contralateral forearm will take place immediately after immersion. The PPT values after the CPT will be divided by PPTs recorded before the test. A value > 1 reflects an analgesic effect due to CPM.

Manual tender point examination

Tender points are typically identified according to the American College of Rheumatology criteria for fibromyalgia.[62] Points can be reliably identified by

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3 application of pressure with the thumb pad of the tester's dominant hand to 18
4 designated sites for 4 seconds until 4 kg (450kPa) of pressure is achieved. Those
5 points where pressure causes pain are summed to give a tender point total.
6 Detecting tender points with digital palpation has good intra-rater reliability and is
7 considered a useful clinical measure for deep tissue hyperalgesia.[63]
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10 11 **Confounding variables**

12 Potentially confounding socio-demographic parameters, including sex, age, marital
13 status, employment status and educational level will be recorded on a standardized
14 form.[19,64,65] Obesity will be measured by recording participants' waist
15 circumference to height ratio.[66]
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18 Other factors known to predict poor outcome in knee OA or influence pain and
19 disability will be accounted for including multiple comorbidities and depressive
20 symptoms.[17] The Centre for Epidemiologic Studies Depression Scale (CES-D) is a
21 valid and reliable measure of depression in community dwelling elderly and a score
22 >16 is considered indicative of depressive symptoms.[67] For each of these variables
23 the method of assessment is detailed in Table 2.
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26 It is inconclusive if radiographic severity has an effect on clinical outcomes and a
27 diagnosis of knee OA can be made clinically without radiographic evidence. For
28 these reasons x-ray results will not be included in the analysis.[68]
29
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31 32 **Patient adherence**

33 Patient adherence to treatment is thought to be an important determinant of clinical
34 outcome in knee OA.[16,69] The physiotherapist will calculate an attendance ratio for
35 each patient.[70,71] Additionally The Sports Injury Rehabilitation Adherence Scale
36 (SIRAS) will be used to measure physiotherapists' perceptions of their patient's
37 rehabilitation adherence at each clinic appointment. In addition to its proven
38 psychometric properties, the SIRAS has been shown to be a reliable scale for use in
39 clinical physiotherapy.[72] The Home Exercise Compliance Assessment (HECA) is a
40 widely used self-report method of assessment to measure adherence. At each
41 physiotherapy appointment participants will record the extent to which they adhered
42 to home exercises and physical activity advice since their previous clinic
43 appointment.[71]
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57 58 **Identifying and quantifying pain sensitization**

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3 Abnormal PPTs and TS have been previously used for identifying sub-groups of
4 patients with widespread pain hypersensitivity.[5,73] Conditioned pain modulation is
5 reflective of the endogenous inhibitory capacity of the nociceptive system and
6 dysfunction of CPM is associated with conditions where central sensitization is a
7 recognised hallmark.[74,75] Hypersensitivity to stimuli assessed at the painful knee
8 reflects peripheral sensitization while hypersensitivity at a distant site is thought to be
9 a consequence of central sensitization.[76] In knee OA joint it can be difficult to
10 distinguish peripheral sensitization from central sensitization as knee OA symptoms
11 are often reported bilaterally therefore testing a local and remote site is deemed
12 appropriate.
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20 Pain sensitization will therefore be operationalized by the presence of decreased
21 PPTs and enhanced TS at local (knee) and remote (arm) sites in addition to
22 dysfunctional CPM. Standardised z-scores for each of these 5 components will be
23 computed for each participant, and compared to QST results from age and gender
24 matched healthy controls. Where PPTs are decreased, TS is enhanced or CPM is
25 dysfunctional in relation to control data points for pain sensitization will be allocated.
26 The cut-off point for what is abnormal or sensitized will be determined when control
27 data has been gathered and the spread or variability of 'normal' results is seen.
28 Points will be summed to produce a pain sensitization score where a higher score
29 will represent greater pain sensitization. This composite score can be used in the
30 logistic regression model. Creation of a pain sensitization index involving
31 amalgamation of QST data has been utilised in previous musculoskeletal
32 research.[77,78]
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41 **Data analysis plan**

42 Data will be analysed using SPSS v 20 (SPSS Inc., Chicago, IL). Descriptive
43 statistics will be calculated for all outcome measures at baseline, including for all
44 continuous variables, means, standard deviations, or medians with ranges of scores;
45 and for categorical variables, frequencies and percentages.
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48 Initial analyses will be exploratory to compare symptom profiles between people who
49 respond to treatment and treatment non-responders. Treatment responders will be
50 categorised by the OMERACT-OARSI responder criteria as described previously.
51 Categorical variables will be analysed using chi-square tests. Multivariate analysis of
52 variance (MANOVA) will be used to compare continuous normally distributed
53 variables between responders and non-responders. The Kruskal-Wallis test will be
54 used for comparison of variables that are not normally distributed. A *p* value of less
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3 than 0.05 will be considered significant. In cases where data is missing a non-
4 responder imputation will be applied (ie. baseline observation carried forwards). A
5 sensitivity analysis will be carried out to assess if this changes the results.
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9 A logistic regression model will be developed to predict response to physiotherapy
10 treatment with 'treatment responder' as the dependant variable. The model will be
11 adjusted for predetermined variables based on the previous literature (age, gender,
12 obesity, socioeconomic status, depressive symptoms, treatment adherence,
13 comorbidities and presence of widespread pain).[17,19,64,65] The pain sensitization
14 score will be entered into the regression model as an independent variable.
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18 **Sample size**

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20 The sample size was calculated based on the number of explanatory variables
21 planned for inclusion in the logistic regression model. It is intended to include 8
22 explanatory variables and allow 15 participants for each explanatory variable.[79]
23 Recruiting 140 participants while allowing for a 20% loss to follow-up should ensure
24 adequate numbers.
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28 **Dropouts**

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30 All participants will be followed up on discharge from physiotherapy. Patients who
31 discontinued treatment will have the opportunity to provide follow-up data. Patients
32 will be considered lost to follow-up if they do not complete the primary outcome
33 measure post treatment.
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37 **ETHICS AND DISSEMINATION**

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39 This study has been approved by St. James's Hospital/AMNCH Research Ethics
40 Committee (ref. no. 2013/11/Chair) and by the St. Vincent's Healthcare Group Ethics
41 and Medical Research Committee (ref. no. HOL/9414) and will be conducted in
42 accordance with the Helsinki Declaration. Fully informed written consent will be
43 obtained and patients incapable of giving full consent will not be recruited.
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47 The study findings will be presented at national and international conferences and
48 will be published in peer-reviewed journals.
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52 **DISCUSSION**

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3 To our knowledge this is the first study to examine the effects of pain sensitization on
4 clinical outcomes in response to physiotherapy in patients with knee OA. The
5 research is exploratory in nature and some limitations are outlined below.

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7 For the purposes of this clinical research the term pain sensitization will be utilised
8 however the lack of a widely accepted definition and criteria for identifying pain
9 sensitization is acknowledged as a limitation.
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12 The QST protocols originally developed for assessing neuropathic pain are
13 lengthy.[31] However if somatosensory testing is to be incorporated into routine
14 clinical practice it must be both time and cost-efficient.[32,86] This study will focus on
15 tests to identify features of pain sensitivity based on their utility and practicality in the
16 clinical setting. However these criteria necessitate the exclusion of certain tests, such
17 as thermal pain thresholds, that are difficult to carrying out reliably in the clinical
18 setting in a limited time frame.
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24 The central concern of this study relates to alterations in pain processing and any
25 potential relationship with poorer prognosis in knee OA. A range of clinical,
26 psychological and socio-demographic predictors of poor outcome have been
27 identified.[81–83] Incorporating all these variables is not feasible and would make for
28 an unacceptably long participant assessment and complex analytical model.
29 Nonetheless the most important predictor variables will be accounted for in the
30 analysis.
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36 This clinically based observational study does not aim to investigate the effects of
37 specific physiotherapy treatments. It will observe people undergoing usual
38 physiotherapy and variation in the intervention is to be expected. Nonetheless an
39 attempt to standardise care to some degree will be made by using current evidence
40 based guidelines and keeping a record of the physiotherapy intervention and
41 adherence for each participant.
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46 Recruiting the participant sample from the secondary care setting will limit the
47 generalizability of study findings to patient populations in primary care. However
48 including only patients from this subgroup is necessary in order to recruit a sufficient
49 number of participants with moderate/severe symptoms.
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52 The analyses reported in this study will be exploratory and generate rather than
53 confirm hypotheses about pain sensitization and physiotherapy for knee OA. It is
54 acknowledged that widespread pain hypersensitivity and somatosensory
55 abnormalities can arise from a host of complex and interacting neurophysiological,
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3 psychological and immunological processes.[20]
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6 Given its relatively short follow-up period we cannot infer causality directly from our
7 data with regard to pain sensitization and physiotherapy outcomes. Nonetheless it
8 may point to a relationship worthy of further investigation in order to better
9 understand pain mechanisms in knee OA and optimise physiotherapy outcomes in
10 the future.
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13 14 15 **Footnotes**

16
17 **Acknowledgements** We would like to acknowledge the Physiotherapy Departments
18 of St. James's Hospital, St. Vincent's University Hospital and Tallaght Hospital,
19 Dublin for agreeing to facilitate this research.
20

21
22 **Competing Interests** The authors declare that they have no competing interests.

23
24 **Funding** This work was supported by a Research Fellowship for Healthcare
25 Professionals from the Health Research Board, Ireland. Grant number:
26 HPF/2013/449.
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28
29 **Authors' Contributions** HOL, CD, KS and NM assisted with the protocol design.
30 CD, KS, NM and HOL procured the project funding. CB provided statistical advice.
31 All authors provided feedback on drafts of the paper and approved the final
32 manuscript.
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35 **Data Sharing Statement** This is a study protocol submission.
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46 Figure Legends

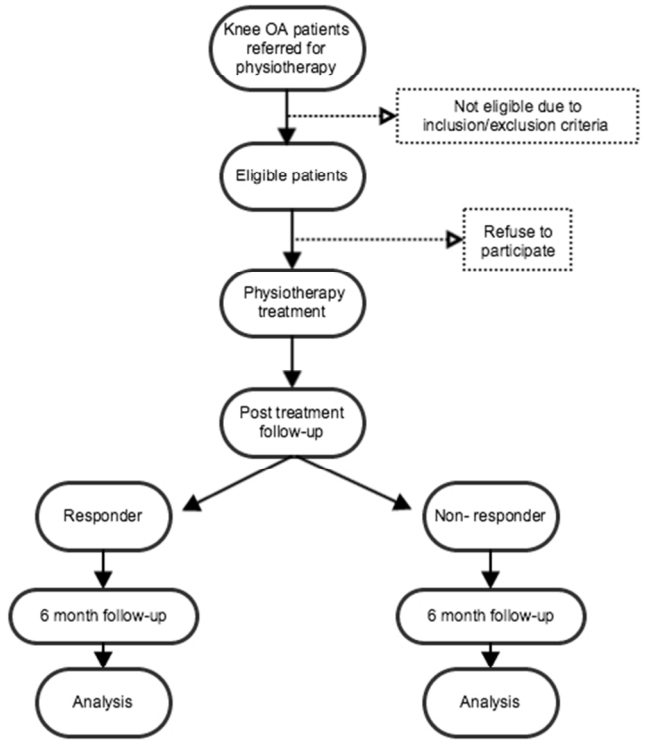
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49 **Figure 1** Flow of participants through the study

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52 **Figure 2** Set of responder criteria [34]
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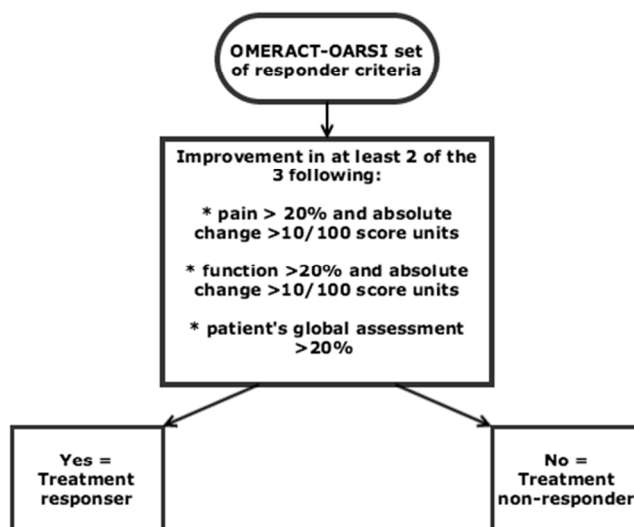
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"Flow of participants through the study"
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"Set of treatment responder criteria "
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4 & 5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6 & 7
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9, 10, 11, 12, 13, 14
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Table 2, 10, 11, 12, 13, 14
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	16
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	15, 16
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	15, 16
		(b) Describe any methods used to examine subgroups and interactions	NA
		(c) Explain how missing data were addressed	16
		(d) If applicable, explain how loss to follow-up was addressed	17
		(e) Describe any sensitivity analyses	17
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations			17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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BMJ Open

Pain sensitization and the risk of poor outcome following physiotherapy for knee osteoarthritis: protocol for a prospective cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-007430.R1
Article Type:	Protocol
Date Submitted by the Author:	02-Apr-2015
Complete List of Authors:	O'Leary, Helen; University College Dublin, School of Public Health, Physiotherapy and Population Science Smart, Keith; St. Vincent's University Hospital, Physiotherapy Department Moloney, Niamh; Macquarie University, Dept of Health Sciences Blake, Catherine; University College Dublin, School of Public Health, Physiotherapy and Population Science Doody, Catherine; University College Dublin, School of Public Health, Physiotherapy and Population Science
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Pain management < ANAESTHETICS

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Pain sensitization and the risk of poor outcome following physiotherapy for
knee osteoarthritis: protocol for a prospective cohort study

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Keywords: knee osteoarthritis, pain, central nervous system sensitization,
physiotherapy

Word count of revised manuscript: 4870

ABSTRACT

Introduction

Pain is the dominant symptom of knee osteoarthritis and recent evidence suggests factors outside of local joint pathology, such as pain sensitization, can contribute significantly to the pain experience. It is unknown how pain sensitization influences outcomes from commonly employed interventions such as physiotherapy.

The aims of this study are firstly to provide a comprehensive description of the somatosensory characteristics of people with pain associated with knee OA. Secondly, we will investigate if indicators of pain sensitization in patients with knee osteoarthritis are predictive of non-response to physiotherapy.

Methods and analysis

This is a multi-centre prospective cohort study with 140 participants. Eligible patients with moderate to severe symptomatic knee osteoarthritis will be identified at outpatient orthopaedic and rheumatology clinics. A baseline assessment will provide a comprehensive description of the somatosensory characteristics of each participant; by means of clinical examination, quantitative sensory testing and validated questionnaires measuring pain and functional capacity. Participants will then undergo physiotherapy treatment. The primary outcome will be non-response to physiotherapy on completion of the physiotherapy treatment programme as defined by the Osteoarthritis Research Society International (OARSI) treatment responder criteria.

Measures of pressure pain thresholds, temporal summation and conditioned pain modulation will be used to create a composite score of pain sensitization. Regression analyses will explore the relationship between responder status and pain sensitization while accounting for confounders.

Ethics and dissemination

This study has been approved by St. James's Hospital/AMNCH Research Ethics Committee and by the St. Vincent's Healthcare Group Ethics and Medical Research Committee. The results will be presented at international conferences and published in a peer review journal.

ARTICLE SUMMARY

Strengths and limitations of this study

To our knowledge this is the first study prospectively examining the effects of pain sensitization on physiotherapy outcomes.

Strengths of this proposed study include the relatively large sample for the comprehensive assessment procedure involved, the use of a broad range of validated measures to study pain processing and the gathering of our own reference QST data from healthy volunteers.

This study will focus on tests to identify features of pain sensitivity based on their utility and practicality in the clinical setting. However these criteria necessitate the exclusion of certain tests, such as thermal pain thresholds, that are difficult to carrying out reliably in the clinical setting in a limited time frame.

As this is a clinically based observational study there is likely to be variation in the duration and type of physiotherapy interventions. The findings of this research may identify clinical and psychophysiological variables predictive of a poor response to physiotherapy that might usefully inform subsequent studies aimed at targeting such variables in an attempt to optimise patients' outcomes.

INTRODUCTION

Knee osteoarthritis (OA) is a prevalent joint disease that causes a huge burden of pain, disability and loss of productivity worldwide.[1–3] With ageing populations and increasing obesity, the prevalence of OA is rising, thus its timely and effective management is a priority within healthcare.[3,4]

The pathophysiology of knee OA pain is complex. Altered processing of nociceptive inputs at peripheral, spinal and higher brain centers may help explain discrepancies between pain severity and the degree of structural and pathological abnormalities in OA.[5–7] Central sensitization is described as an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input,[8] and can manifest clinically as general pain hypersensitivity.[9] Furthermore, peripheral pro-inflammatory mediators and neuropeptides in knee OA can sensitize nociceptors in the affected knee, lowering their threshold for activation.[10] This increased responsiveness of nociceptive neurons is referred to as peripheral sensitization.[8]

Both peripheral and central sensitization, clinically referred to as pain sensitization, can contribute to painful knee OA. Pain sensitization may be useful as a clinical construct to alert clinicians to patients with a potentially upregulated nociceptive state and is proposed to contribute to an enhanced, persistent and more widespread pain response.[11] Recent studies in knee OA have found the presence of increased pain sensitivity at remote sites, enhanced temporal summation (TS) and hypersensitivity to various stimuli to be associated with reports of more severe symptoms.[5,6,12] However these cross-sectional studies linking features of sensitization to greater levels of pain and disability do not explore if pain sensitivity has any prognostic implications.

There is also some evidence to suggest increased pain sensitivity negatively affects treatment outcomes. In painful musculoskeletal conditions such as shoulder impingement and lateral epicondylalgia widespread pressure pain sensitivity and thermal hyperalgesia, have been linked with a poorer prognosis.[13,14] Surgical outcomes for knee osteoarthritis may also be affected, with the presence of increased pain sensitivity prior to total knee replacement associated with more persistent pain after surgery.[15,16]

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3 Although joint replacement is considered an effective treatment for end-stage knee
4 OA, the majority of patients are managed conservatively. Physiotherapy is the widely
5 recommended conservative treatment approach for knee OA.[17] Existing studies of
6 prognosis in knee OA have focused on demographic and psychological
7 variables.[18–20] Whilst it has been suggested that central pain processing may
8 contribute significantly to the clinical pain experience in some people with knee
9 OA[21], no longitudinal studies have explored the potentially negative prognostic
10 impact of pain sensitization on outcomes in response to physiotherapy. In whiplash
11 associated disorders the presence of sensory hypersensitivity and cold hyperalgesia
12 has been shown to reduce the likelihood of a positive response to physiotherapy
13 treatment.[22] Thus it is conceivable, but currently unproven, that knee OA patients
14 with evidence of pain sensitization have poorer outcomes following physiotherapy.
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22 One obstacle to investigating the implications of pain sensitization is reliably
23 identifying it in the clinical setting. Due to the complexity of pain mechanisms it is
24 inadvisable to rely on any single test to reflect peripheral and central pain
25 mechanisms.[23,24] A multi-tissue assessment using a multi-modal stimuli approach
26 has been advocated,[25], and will be adopted in this study. Three constructs will be
27 combined into a single score encompassing key features of pain sensitization
28 previously identified in knee OA patients. [6,11,26] Composite pain sensitivity scores
29 have recently been used to investigate its association with clinical characteristics.
30 Our study will be the first to prospectively explore the effect of pain sensitization on
31 clinical outcomes.
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39 This study will investigate the extent to which (a composite measure of) pain
40 sensitization predicts non-response to physiotherapy in patients with knee OA.
41 Identifying clinical and psychophysical features of pain sensitization in knee OA
42 predictive of a poor response to physiotherapy might help inform the management of
43 such patients. It may invite clinicians to consider additional or alternative
44 interventions aimed at reducing such pain sensitization and optimise outcomes.
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48 **Study aims**

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50 The main aims of the study are; firstly to provide a comprehensive description of the
51 somatosensory characteristics of people with pain associated with knee OA (by
52 means of quantitative sensory testing (QST), and validated questionnaires
53 measuring pain, functional capacity and quality of life) and secondly, to investigate if
54 the presence of pain sensitization at baseline is predictive of non-response to
55 physiotherapy treatment as defined by treatment responder criteria.
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We hypothesise that the presence of pain sensitization will predict a non-response to physiotherapy treatment compared to patients without evidence of pain sensitization.

METHODS AND ANALYSIS

Study design

A multi-centre observational cohort study with assessments at baseline, post-treatment and at six months will be conducted. Following the baseline assessment for features of pain sensitization all participants will receive usual physiotherapy care. The relationship between pain sensitization and outcomes in terms of pain and disability will be explored through regression analysis.

Setting

The study will be undertaken in the physiotherapy outpatient departments of three large publicly funded university teaching hospitals in Dublin, Ireland.

Participants

Patients with symptomatic knee OA,[27], referred for physiotherapy treatment by a hospital consultant or clinical specialist physiotherapist will be eligible for inclusion. Full details of inclusion/exclusion criteria are summarised in Table 1.

At the time of recruitment knee pain must be the participant's primary musculoskeletal complaint for which they are seeking treatment, and physiotherapy must be the main treatment being undertaken over the study period. Participants recruited at physiotherapy led musculoskeletal assessment clinics will be screened for eligibility by the clinical specialist physiotherapist. The principal investigator will screen patients on the physiotherapy waiting list over the telephone.

Table 1. Study inclusion and exclusion criteria

Inclusion Criteria	
Diagnosis	Knee osteoarthritis based on American College of Rheumatology clinical criteria [27] and confirmed by radiographic findings
Age	Over 50 years
Pain duration	Knee pain for at least 6 months
Severity	Pain \geq 5/10 on Numerical Rating Scale
Medication	Willing to abstain from simple analgesics and NSAIDs for 24 hours prior to testing

Consent	Willing and able to give full consent
Exclusion Criteria	
Pathology	Lumbar or cervical radiculopathy, systematic inflammatory disease, positive screen for diabetic neuropathy, neuropathic pain
Past medical history	Previous surgery or disease of the peripheral or central nervous system, sensory loss secondary to chemotherapy or radiotherapy, fibromyalgia, chronic fatigue syndrome
Cognitive ability	Cognitive or psychiatric disorder interfering with ability to fully consent or cooperate with assessment
Other treatment	Injection or physiotherapy treatment for knee joint within previous 3 months
Medication	Taking anti-depressant or anti-convulsant medication

Healthy controls

Healthy participants are defined as people with no current pain or chronic pain problems in the past year. Forty age and gender matched controls will be recruited from the general population, and from the staff and student population in University College Dublin. The controls will provide reference data for QST results.

Investigator

The principal investigator, (HOL) collecting all baseline and follow-up data, will be a senior physiotherapist with twelve years clinical experience. The same investigator will carryout all tests and is trained in using QST.

Recruitment procedure

A consecutive sample of knee OA patients with moderate/severe knee pain (defined as self-reported pain of ≥ 5 on an 11-point numerical rating scale) will be recruited. Between June 2014 and July 2015 potentially eligible participants will be identified at musculoskeletal assessment clinics and from physiotherapy outpatient waiting lists. A feasible recruitment rate is estimated at 12 patients per month with recruitment continuing until the specified numbers are achieved. Those who agree to participate will attend for an assessment prior to commencing physiotherapy treatment. Written informed consent will be obtained before enrolment in the study. Figure 1 represents the flow of participants through the study.

Physiotherapy management

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Physiotherapy treatment will be in line with current clinical guidelines for the management of knee OA.[28] Treatment will typically involve between four and six physiotherapy appointments. In some cases treatment may take the format of a small group exercise intervention. A workshop led by the principal investigator will be held at each recruitment site prior to study commencement where physiotherapists will receive an update on clinical guidelines and current best evidence on management of knee OA. This will standardise treatment to some degree, but intervention will be individualised at the discretion of the treating physiotherapist and in consultation with the patient.

Assessment

Baseline assessment

A schematic view of the outcome measures recorded at baseline and follow up is presented in Table 2. Each assessment will take approximately one hour to complete. Some questionnaires will be posted and completed in advance by participants.

Follow up assessment

The primary endpoint will be at completion of physiotherapy treatment, this time point is estimated to be on average at 3 months. Physiotherapy administration staff will alert the principal investigator when a participant is discharged. Thereupon pain, disability and global rating of change will be assessed by means of a postal questionnaire. Information will also be recorded on use of co-interventions or any change in medication for knee pain. This follow-up questionnaire will be administered 1 week of discharge from physiotherapy.

Six months after enrolment into the study, participants will complete a postal questionnaire assessing pain and function. They will exit the study at this point.

Assessment procedures and minimising bias

Studies support the reliability of QST measures where protocols are standardised and both the tester and participant are carefully instructed.[25] Standardised assessment procedures will be followed in this study. At each location testing will be undertaken in the same temperature controlled room by the same investigator, using a single set of testing devices. Each session will begin by familiarising participants with standardised test procedures.[29,30] Physical testing will be performed by the investigator prior to in-depth subjective assessment or without knowledge of questionnaire scores. Test order is important,[31], and a pre-determined sequence

will be used beginning with non-noxious stimuli. CPM can induce a residual effect and will be the final test.[32] With bilateral symptoms the most painful knee will be selected, if both are equally symptomatic the right knee will be tested. Where shoulder pain is present unilaterally the opposite forearm will be used for testing.

Table 2. Outcome measures and collection points

Domain	Variable	Instrument for Data Collection	Collection Points
Demographics	Age, Gender, Educational attainment, Employment status, Marital status	Baseline assessment questionnaire	Baseline
Pain	Self reported pain	WOMAC pain sub-scale	Baseline, post treatment*, 6 months
	Pain intensity	Numerical rating scale	Baseline, 6 months
	Location & quality	Knee Pain Map	Baseline
	Neuropathic pain symptoms	Modified PainDETECT	Baseline
	Characteristics of osteoarthritic pain	Intermittent and Constant Osteoarthritis Pain Instrument	Baseline
	Widespread pain	Body chart Manual tender point count	Baseline
Function	Self reported function	WOMAC function sub-scale	Baseline, post treatment, 6 months
Quality of life	Health related quality of life	EQ-5D 5L	Baseline
Central Sensitization Symptoms	Non-musculoskeletal central sensitization symptoms	Central Sensitization Inventory	Baseline
Quantitative Sensory Testing	Light touch	Von Frey filaments	Baseline
	Vibration	Graded tuning fork	Baseline
	Pain pressure thresholds	Pressure algometry	Baseline
	Dynamic allodynia	Brush stroke	Baseline
	Static allodynia	Von Frey Filaments	
	Thermal hyperalgesia	Thermo-rollers	Baseline
	Temporal summation	Repetitive mechanical stimuli with weighted pinprick	Baseline
	Conditioned pain modulation	Cold pressor test	Baseline
Confounding Variables	Obesity	Ratio of waist circumference to height	Baseline
	Depressive symptoms	Centre for Epidemiologic	Baseline

		Studies Depression Scale	
	Comorbidities	Self Administered Comorbidity Questionnaire	Baseline
Management related variables	Treatment adherence	Sports Injury Rehabilitation Adherence Scale	During treatment
		Patient attendance ratio	During treatment
		Home Exercise Compliance Assessment	During treatment
	Treatment type and duration, Adverse effects	Therapist record sheet	During treatment
	Medication use and co-interventions	Follow-up questionnaire	Post treatment, 6 months
Treatment outcome	Response to treatment	OARSI Responder Criteria; WOMAC pain and function subscales, global rating of change	Post treatment

* Post treatment assessment will be at approximately 3 months

Primary outcome variable

The main outcome is response to physiotherapy treatment and this will be determined using a set of responder criteria by the Outcome Measures in Rheumatology - Osteoarthritis Research Society International (OMERACT-OARSI).[33] Non-response to physiotherapy will be the designated categorical dependent variable upon which the subsequent regression analyses will be based.

The responder criteria will be applied to the relevant data gathered at post treatment follow-up and are summarised in Figure 2. For application of these criteria pain and function will be measured with the subscales of the Western Ontario and McMasters University Score Osteoarthritis Index (WOMAC LK 3.0). Validity and reliability of these subscales are well established, including for postal surveys.[34–36] Global rating of change will be measured with a 7-point Likert scale. This scale captures relevant change by asking the patient about any improvement or deterioration that has occurred with physiotherapy treatment.[37] Two points on the scale represents a 20% improvement.

Secondary outcome variables

Pain assessment

The following valid and reliable measures of pain will be recorded; The Pain Intensity Numerical Rating Scale (Pain NRS) will measure participant's average pain intensity

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3 over the previous seven days.[38,39] The Knee Pain Map will be used to record
4 more detailed information about the location and quality of knee pain.[40]
5 Widespread pain is defined for this study according to the American College of
6 Rheumatology classification criteria using pain drawings marked by participants on a
7 body manikin.[41] Widespread pain is associated with more severe knee pain and
8 functional decline.[42,43]
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12 **Pain and quality of life questionnaires**

13 *Modified PainDETECT (mPD-Q)*

14 This questionnaire will record any neuropathic component to participants' symptoms.
15 It has been previously used for the screening of neuropathic pain-like symptoms in
16 knee OA in an elderly cohort.[44] Participants with more neuropathic pain-like
17 symptoms (scores > 12/38) are more likely to have signs of central sensitisation.[45]
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24 *Intermittent and Constant Osteoarthritis Pain Instrument (ICOAP)*

25 This validated questionnaire assesses various facets of both intermittent and
26 constant pain for the knee, including effects on sleep and quality of life, degree of
27 frustration and worry associated with the pain.[46] Two predictability items will be
28 administered to capture unpredictable spontaneous pain, thought to have the
29 greatest impact on participant well-being.[47]
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35 *Central Sensitization Inventory (CSI)*

36 This self-report inventory has preliminary validity and reliability and assesses for
37 symptoms not related to the musculoskeletal system but common to central
38 sensitization syndromes.[48,49] Good sensitivity (81%) and specificity (79%) values
39 were found with a cut-off score of 40 (out of 100) to identify patients with symptoms
40 of central sensitization.[49]
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45 *EuroQoL EQ-5D*

46 The EQ-5D is a frequently used generic quality of life instrument, designed by the
47 EuroQoL group.[50] A modified form has been developed with an enlarged number
48 of possible answers to avoid a ceiling effect.[51] The EQ-5D has acceptable reliability
49 and validity when used in patients with knee OA.[52]
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55 **Quantitative Sensory Testing (QST)**

56 QST is a psychophysiological measure of perception in response to external stimuli
57 of controlled intensity.[30] This QST protocol will make reference to the well-
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3 established German Neuropathic Pain Consortium (DFNS) protocol,[30], and will
4 utilise clinical QST methods recommended by the International Association for the
5 Study of Pain.[29] This current study's assessment protocol aims to be more
6 accessible using tools that are relatively inexpensive and adaptable to the clinical
7 setting.[53] Test sites used will be as follows; *Site 1*: On the medial or lateral knee
8 joint line, depending where the patient indicates their greatest pain (3 cm medial to
9 medial edge of patella or corresponding site laterally), *Site 2*: Over ipsilateral tibialis
10 anterior muscle (5 cm distal to the tibial tuberosity), *Site 3*: On the contralateral
11 forearm (5 cm distal to lateral epicondyle of humerus on the volar aspect).
12 Somatosensory abnormalities over the area of *Site 2* tibialis anterior are thought to
13 provide evidence of spreading sensitization from the symptomatic knee. Changes at
14 *Site 3* could indicate more widespread sensitization at a generalised level in the
15 central nervous system,[11], although this can not be concluded definitively as other
16 explanations for abnormal QST results outside the knee are also possible, for
17 example patients with knee OA frequently have multi-site pain.[42]

27 *Light touch*

28 Mechanical detection thresholds will be tested using a set of von Frey filaments
29 (Opti-hair2-Set, Marstock, Germany). Monofilaments beginning with the smallest
30 diameter will be applied to the skin. Light touch threshold (gm/mm^2) will be recorded
31 as the last filament (gm/mm^2) that can be perceived. Test-retest reliability of this
32 method for knee OA has been established.[54]

37 *Mechanical allodynia*

38 Dynamic mechanical allodynia will be assessed by lightly stroking the knee and
39 forearm with a brush stroke three times (Senselab Brush No 5, Somedic). Static
40 allodynia will be assessed using von Frey filaments. The presence of mechanical
41 allodynia will be recorded if this non-noxious stimulation evokes a sensation of
42 pain.[55]

47 *Thermal hyperalgesia*

48 Thermal rollers with predetermined temperatures of 25°C (cold) and 40°C (warm)
49 (Senselab Rolltemp Somedic) will be used to detect thermal hyperalgesia at the
50 forearm and knee.[53] Participants will be asked to report if the thermal sensation is
51 perceived as painful when the rollers are passed lightly over the skin.

57 *Vibration*

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3 Vibration detection threshold will be measured with a graded tuning fork (Rydel–
4 Seiffer, 64 Hz) placed over 3 bony prominences (ulnar styloid, patella and medial
5 malleolus). Vibration detection threshold is determined as a mean disappearance
6 threshold of the vibrations on an 8/8 scale with the stimulus repeated three times.[30]
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10 *Pressure pain thresholds (PPTs)*

11 Pressure will be applied using an electronic digital algometer with a probe size of 1
12 cm² (SomedicAB, Sweden) and an application rate of 30 kPa/s. The participant will
13 be instructed to press an automatic cut off button when the first sensation of pressure
14 pain is perceived. A cut-off point is set at 1000kPa. PPTs will be measured 3 times at
15 the 3 test sites; the first measurement will be excluded and the mean of the last two
16 measurements will be used for analysis. Test-retest reliability using this technique
17 has been demonstrated in patients with knee OA.[56]
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24 *Mechanical temporal summation (TS)*

25 The participant will assign a pain rating to a single stimulus by a weighted pinprick
26 (MRC Systems 256 mN) and for a series of 10 pinprick stimuli of the same intensity
27 (1/s applied within an area of 1 cm²).[57] This procedure will be applied twice on a
28 marked area the forearm and knee site. The mean pain rating of the pinprick trains
29 minus the mean pain rating of the single stimuli will give a value for TS.[58,59]
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35 *Conditioned pain modulation (CPM)*

36 The cold pressor test is recommended for assessment of CPM in the clinical setting.
37 [60,61] The test stimulus will be PPT, while the conditioning stimulus will be cold
38 immersion. PPTs will be recorded as outlined above. With the participant seated
39 comfortably, the opposite arm to that used for PPT testing will be immersed in a bath
40 of icy water (4°C monitored by thermometer) up to the elbow for 60 seconds.
41 Participants unable to tolerate the water bath will rate their pain before withdrawing
42 the arm (aim for at least 5 on NRS).[32] Re-testing of PPTs on the contralateral
43 forearm will take place immediately after immersion. The PPT values after the cold
44 pressor test will be divided by PPTs recorded before the test. A value of < 1 will be
45 taken to reflect pain facilitation due to an inefficient CPM response.
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53 **Manual tender point examination**

54 Tender points are typically identified according to the American College of
55 Rheumatology criteria for fibromyalgia.[62] Points can be reliably identified by
56 application of pressure with the thumb pad of the tester's dominant hand to 18
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3 designated sites for 4 seconds until 4 kg (450kPa) of pressure is achieved. Those
4 points where pressure causes pain are summed to give a tender point total.
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6 Detecting tender points with digital palpation has good intra-rater reliability and is
7
8 considered a useful clinical measure for deep tissue hyperalgesia.[63]
9

10 **Patient adherence**

11 Patient adherence to treatment is thought to be an important determinant of clinical
12 outcome in knee OA.[17,64] The physiotherapist will calculate an attendance ratio for
13 each patient.[65,66] Additionally The Sports Injury Rehabilitation Adherence Scale
14 (SIRAS) will be used to measure physiotherapists' perceptions of their patient's
15 rehabilitation adherence at each clinic appointment. In addition to its proven
16 psychometric properties, the SIRAS has been shown to be a reliable scale for use in
17 clinical physiotherapy.[67] The Home Exercise Compliance Assessment (HECA) is a
18 widely used self-report method of assessment to measure adherence. At each
19 physiotherapy appointment participants will record the extent to which they adhered
20 to home exercises and physical activity advice since their previous clinic
21 appointment.[66]
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30 **Confounding variables**

31 Potentially confounding socio-demographic parameters, including age, gender,
32 marital status, employment status and educational level will be recorded on a
33 standardized form.[20,68,69] Obesity will be measured by recording participants'
34 waist circumference to height ratio.[70]
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40 Other factors known to predict poor outcome in knee OA or influence pain and
41 disability will be accounted for including multiple comorbidities and depressive
42 symptoms.[18] The Centre for Epidemiologic Studies Depression Scale (CES-D) is a
43 valid and reliable measure of depression in community dwelling elderly and a score
44 >16 is considered indicative of depressive symptoms.[71] For each of these variables
45 the method of assessment is detailed in Table 2.
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50 The presence of widespread pain is another potential confounder,[42] however it
51 could also be a mediator between pain sensitization and QST measures such as
52 lowered PPTs remotely. For this reason the regression model will not be adjusted for
53 this variable.
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3 Radiographic severity of knee OA is poorly correlated with self-reported pain and
4 pain sensitization. [5,6] For these reasons x-ray results will not be included in the
5 analysis.[72]
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8 **Defining pain sensitization**

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10 In order to describe the somatosensory characteristics z-scores will be calculated for
11 individual OA patients. The control group will provide reference data for QST results
12 and enable calculation of a standardised z-score using the following formula:

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$$z = (\text{value}_{\text{participant}} - \text{mean}_{\text{controls}}) / \text{standard deviation}_{\text{controls}}$$
 [30] Calculating the z-score
14 for each QST modality and body site facilitates the comparison of QST results with
15 healthy control subjects independent of the unit of measure. Any z-score outside the
16 10th and 90th percentile (or 1.28 standard deviations of the mean) is classified as
17 abnormal.
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24 Abnormal PPTs and TS have been previously used for identifying sub-groups of
25 patients with widespread pain hypersensitivity.[5,73] Conditioned pain modulation is
26 reflective of the endogenous inhibitory capacity of the nociceptive system and
27 dysfunction of CPM is associated with conditions where central sensitization is a
28 recognised hallmark.[74,75] Pain sensitization will therefore be operationalized using
29 five QST results; PPTs (forearm and knee), TS (forearm and knee) and CPM.
30 Abnormally decreased PPTs will be determined by the cut-off point described above.
31 For an individual to be classified as having enhanced TS their absolute score needs
32 to be > 1. For CPM a facilitatory response (where the calculated ratio is < 1) will be
33 classified as an 'abnormal' or dysfunctional. Where PPTs are abnormally decreased,
34 TS is enhanced or CPM is dysfunctional a single data point for each component will
35 be allocated. The points from these 5 components will be summed to produce a pain
36 sensitization score, where a higher score (maximum of 5) will represent greater pain
37 sensitization. This composite score will be used in the logistic regression model.
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39 Creation of a pain sensitization score involving amalgamation of QST data has been
40 utilised in previous musculoskeletal research.[76,77]
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50 **Data Analysis Plan**

51 To address the first aim descriptive statistics will be calculated for all outcome
52 measures at baseline, including for all continuous variables, means, standard
53 deviations, or medians with ranges of scores; and for categorical variables,
54 frequencies and percentages. In summarising descriptive QST data, z-score
55 calculations and cut-off points will determine the prevalence of somatosensory
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3 abnormalities in pressure pain thresholds, mechanical detection threshold, and
4 vibration threshold. Somatosensory abnormalities such as allodynia or thermal
5 hyperalgesia will be classified as either present or absent.
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9 Initial analyses for the second aim will be exploratory to compare symptom profiles
10 between people who respond to treatment and treatment non-responders. These will
11 be categorised by the OMERACT-OARSI responder criteria as described previously.
12 Categorical variables will be analysed using chi-square tests. Multivariate analysis of
13 variance (MANOVA) will be used to compare continuous normally distributed
14 variables between responders and non-responders, and from this variables
15 associated with responder status will be identified. The Mann Whitney test will be
16 used for comparison of variables that are not normally distributed. In cases where
17 data is missing multiple imputations will be applied. A sensitivity analysis will be
18 carried out to assess if this changes the results. A logistic regression model will be
19 developed to predict non-response to physiotherapy treatment with 'treatment non-
20 responder' (yes/no) as the dependant variable. Variables will be chosen for inclusion
21 in the first model iteration if they are found to be associated with non-responder
22 status in uni-variate analysis with a threshold of $p < 0.05$, or if their inclusion is
23 supported by previous literature. The model will be adjusted for predetermined
24 variables such as age, gender, obesity, socioeconomic status, depressive symptoms,
25 treatment adherence and comorbidities.[18,20,68,69] The pain sensitization score
26 will be entered into the regression model as an independent variable. It is anticipated
27 that the regression model will accommodate a maximum of 7 variables with statistical
28 significance accepted if $p < 0.05$. The best fitting and most parsimonious model will be
29 selected as the final iteration and cross validation of the predictive model will be
30 performed.[78] A secondary sub-analysis will explore the ability of some individual
31 QST modalities to predict non-response to physiotherapy if entered into the
32 regression model as single variables.
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35 Data will be analysed using SPSS v 20 (SPSS Inc., Chicago, IL) and R v 3.0.2.
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38 **Sample size**

39 The sample size is calculated based on the number of anticipated explanatory
40 variables planned for inclusion in the logistic regression model. It is expected that a
41 maximum of 7 explanatory variables will be included and 10 cases i.e. non-
42 responders will be allowed for each explanatory variable.[79] It is estimated that 60%
43 of patients will be classified as non-responders to physiotherapy by the OMERACT-
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OARSI criteria.[80] Recruiting 140 participants while allowing for a 15% loss to follow-up should ensure adequate numbers.

Dropouts

All participants will be followed up on discharge from physiotherapy. Patients who discontinued treatment will have the opportunity to provide follow-up data. Patients will be considered lost to follow-up if they do not complete the primary outcome measure post treatment.

ETHICS AND DISSEMINATION

This study has been approved by St. James's Hospital/AMNCH Research Ethics Committee (ref. no. 2013/11/Chair) and by the St. Vincent's Healthcare Group Ethics and Medical Research Committee (ref. no. HOL/9414) and will be conducted in accordance with the Helsinki Declaration. Fully informed written consent will be obtained and patients incapable of giving full consent will not be recruited.

The study findings will be presented at national and international conferences and will be published in peer-reviewed journals.

DISCUSSION

To our knowledge this is the first study to examine the effects of pain sensitization on clinical outcomes in response to physiotherapy in patients with knee OA. The research is exploratory in nature and some limitations are outlined below. For the purposes of this clinical research the term pain sensitization will be utilised however the lack of a widely accepted definition and criteria for identifying pain sensitization is acknowledged as a limitation.

This study will use TS and CPM responses as indicators of pain sensitization, however it is recognised that enhanced TS and dysfunctional CPM also occur in healthy populations,[59,61] and due to the natural variability in responses there is a likelihood of capturing false positives. To account for this only those falling outside the 10th and 90th percentile will be categorised as 'abnormal' and no individual QST modality will be used as a stand-alone measure of pain sensitization.

The QST protocols originally developed for assessing neuropathic pain are lengthy.[30] However if somatosensory testing is to be incorporated into routine clinical practice it must be both time and cost-efficient.[81] This study will focus on tests to identify features of pain sensitivity based on their utility and practicality in the

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3 clinical setting. However these criteria necessitate the exclusion of certain tests, such
4 as thermal pain thresholds, that are difficult to carrying out reliably in the clinical
5 setting in a limited time frame.
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9 The central concern of this study relates to alterations in pain processing and any
10 potential relationship with poorer prognosis in knee OA. A range of clinical,
11 psychological and socio-demographic predictors of poor outcome have been
12 identified.[82–84] Incorporating all these variables is not feasible and would make for
13 an unacceptably long participant assessment and complex analytical model.
14 Nonetheless the most important predictor variables will be accounted for in the
15 analysis.
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20 This clinically based observational study does not aim to investigate the effects of
21 specific physiotherapy treatments. It will observe people undergoing usual
22 physiotherapy and variation in the intervention is to be expected. Nonetheless an
23 attempt to standardise care to some degree will be made by using current evidence
24 based guidelines and keeping a record of the physiotherapy intervention and
25 adherence for each participant.
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30 Recruiting the participant sample from the secondary care setting will limit the
31 generalizability of study findings to patient populations in primary care. However
32 including only patients from this subgroup is necessary in order to recruit a sufficient
33 number of participants with moderate/severe symptoms.
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37 The analyses reported in this study will be exploratory and generate rather than
38 confirm hypotheses about pain sensitization and physiotherapy for knee OA. It is
39 acknowledged that widespread pain hypersensitivity and somatosensory
40 abnormalities can arise from a host of complex and interacting neurophysiological,
41 psychological and immunological processes.[21]
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46 Given its relatively short follow-up period we cannot infer causality directly from our
47 data with regard to pain sensitization and physiotherapy outcomes. Nonetheless it
48 may point to a relationship worthy of further investigation in order to better
49 understand pain mechanisms in knee OA and optimise physiotherapy outcomes in
50 the future.
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55 FOOTNOTES

56 **Acknowledgements** We would like to acknowledge the Physiotherapy Departments
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2
3 of St. James's Hospital, St. Vincent's University Hospital and Tallaght Hospital,
4 Dublin for agreeing to facilitate this research.

5
6 **Competing Interests** The authors declare that they have no competing interests.

7
8 **Funding** This work was supported by a Research Fellowship for Healthcare
9 Professionals from the Health Research Board, Ireland. Grant number:
10 HPF/2013/449.

11
12 **Authors' Contributions** HOL, CD, KS and NM assisted with the protocol design.
13 CD, KS, NM and HOL procured the project funding. CB provided statistical advice.
14 All authors provided feedback on drafts of the paper and approved the final
15 manuscript.
16

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18 **Data sharing statement** It is the intention of the study group, that once the study is
19 completed, and the research articles arising from the study have been published, any
20 data that is fully anonymised and not sensitive would be made open access.
21 However because this intention was not declared in the original ethical applications
22 this action would be subject to approval by the relevant research ethics committees.
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Figure Legends

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51 **Figure 1** Flow of participants through the study
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54 **Figure 2** Set of responder criteria [33]
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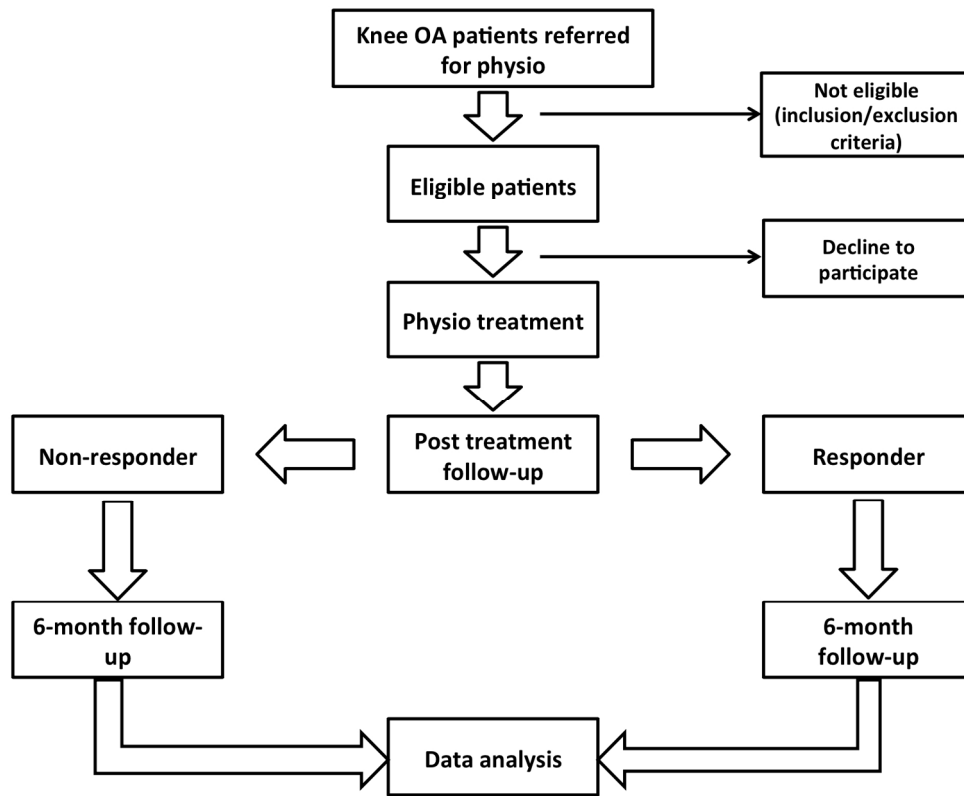


Figure 1 Flow of participants through the study

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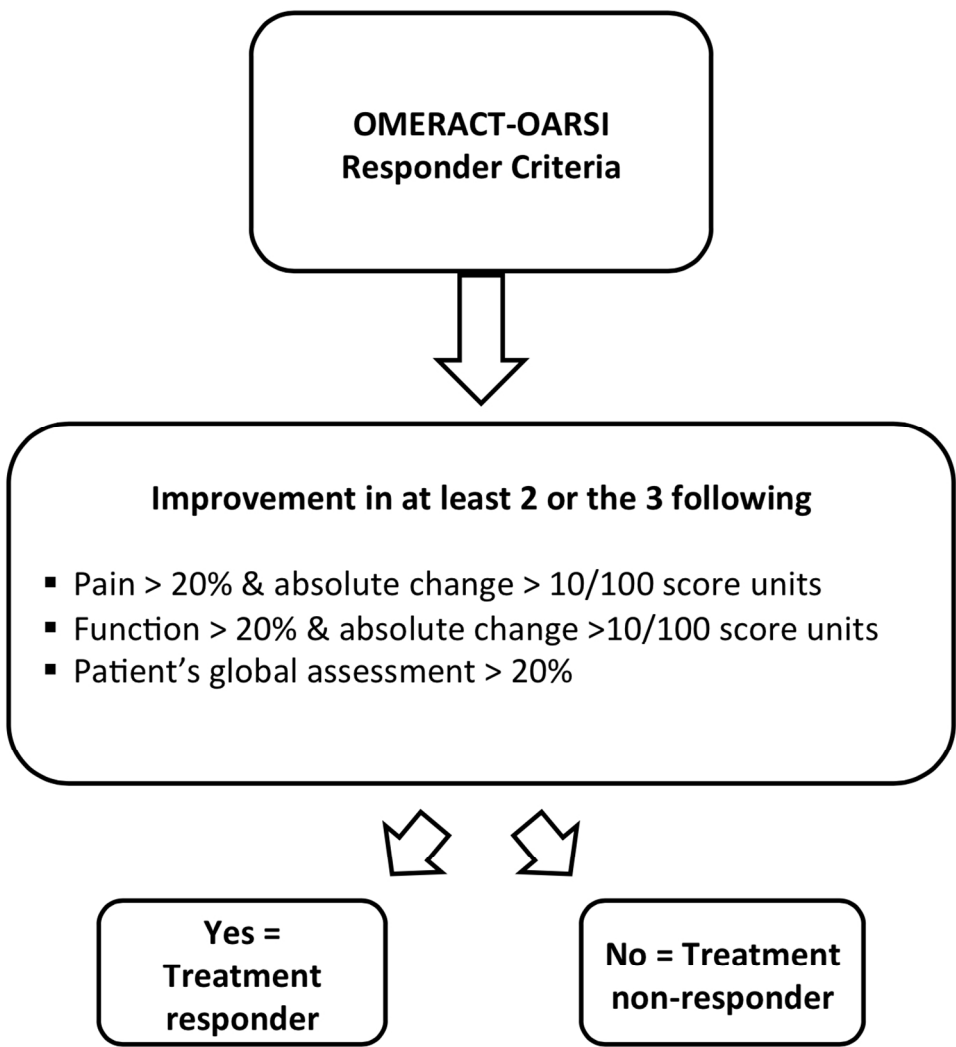


Figure 2 Set of treatment responder criteria [33]

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4 & 5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6 & 7
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9, 10, 11, 12, 13, 14
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Table 2, 10, 11, 12, 13, 14
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	16
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	15, 16
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	15, 16
		(b) Describe any methods used to examine subgroups and interactions	NA
		(c) Explain how missing data were addressed	16
		(d) If applicable, explain how loss to follow-up was addressed	17
		(e) Describe any sensitivity analyses	17
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations			17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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BMJ Open

Pain sensitization and the risk of poor outcome following physiotherapy for patients with moderate to severe knee osteoarthritis: protocol for a prospective cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-007430.R2
Article Type:	Protocol
Date Submitted by the Author:	21-May-2015
Complete List of Authors:	O'Leary, Helen; University College Dublin, School of Public Health, Physiotherapy and Population Science Smart, Keith; St. Vincent's University Hospital, Physiotherapy Department Moloney, Niamh; Macquarie University, Dept of Health Sciences Blake, Catherine; University College Dublin, School of Public Health, Physiotherapy and Population Science Doody, Catherine; University College Dublin, School of Public Health, Physiotherapy and Population Science
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Pain management < ANAESTHETICS

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3 Pain sensitization and the risk of poor outcome following physiotherapy for
4 patients with moderate to severe knee osteoarthritis: protocol for a
5 prospective cohort study
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8 O'Leary H, Smart KM, Moloney NA, Blake C and Doody CM.
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35 Keywords: knee osteoarthritis, pain, central nervous system sensitization,
36 physiotherapy
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38 Word count of revised manuscript: 4870
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ABSTRACT

Introduction

Pain is the dominant symptom of knee osteoarthritis and recent evidence suggests factors outside of local joint pathology, such as pain sensitization, can contribute significantly to the pain experience. It is unknown how pain sensitization influences outcomes from commonly employed interventions such as physiotherapy.

The aims of this study are firstly to provide a comprehensive description of the somatosensory characteristics of people with pain associated with knee OA. Secondly, we will investigate if indicators of pain sensitization in patients with knee osteoarthritis are predictive of non-response to physiotherapy.

Methods and analysis

This is a multi-centre prospective cohort study with 140 participants. Eligible patients with moderate to severe symptomatic knee osteoarthritis will be identified at outpatient orthopaedic and rheumatology clinics. A baseline assessment will provide a comprehensive description of the somatosensory characteristics of each participant; by means of clinical examination, quantitative sensory testing and validated questionnaires measuring pain and functional capacity. Participants will then undergo physiotherapy treatment. The primary outcome will be non-response to physiotherapy on completion of the physiotherapy treatment programme as defined by the Osteoarthritis Research Society International (OARSI) treatment responder criteria.

A principal component analysis will identify measures related to pain sensitization to include in the predictive model. Regression analyses will explore the relationship between responder status and pain sensitization while accounting for confounders.

Ethics and dissemination

This study has been approved by St. James's Hospital/AMNCH Research Ethics Committee and by the St. Vincent's Healthcare Group Ethics and Medical Research Committee. The results will be presented at international conferences and published in a peer review journal.

ARTICLE SUMMARY

Strengths and limitations of this study

To our knowledge this is the first study prospectively examining the effects of pain sensitization on physiotherapy outcomes.

Strengths of this proposed study include the relatively large sample for the comprehensive assessment procedure involved, the use of a broad range of validated measures to study pain processing and the gathering of our own reference QST data from healthy volunteers.

This study will focus on tests to identify features of pain sensitivity based on their utility and practicality in the clinical setting. However these criteria necessitate the exclusion of certain tests, such as thermal pain thresholds, that are difficult to carrying out reliably in the clinical setting in a limited time frame.

As this is a clinically based observational study there is likely to be variation in the duration and type of physiotherapy interventions. The findings of this research may identify clinical and psychophysiological variables predictive of a poor response to physiotherapy that might usefully inform subsequent studies aimed at targeting such variables in an attempt to optimise patients' outcomes.

INTRODUCTION

Knee osteoarthritis (OA) is a prevalent joint disease that causes a huge burden of pain, disability and loss of productivity worldwide.[1–3] With ageing populations and increasing obesity, the prevalence of OA is rising, thus its timely and effective management is a priority within healthcare.[3,4]

The pathophysiology of knee OA pain is complex. Altered processing of nociceptive inputs at peripheral, spinal and higher brain centers may help explain discrepancies between pain severity and the degree of structural and pathological abnormalities in OA.[5–7] Central sensitization is described as an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input.[8] It can have widespread effects such general pain hypersensitivity while other regional manifestations of central sensitization include spread of pain sensitivity to normal tissue, an exaggerated response to a noxious stimulus and pain after the end of a stimulus. [9] Furthermore, peripheral pro-inflammatory mediators and neuropeptides in knee OA can sensitize nociceptors in the affected knee, lowering their threshold for activation.[10] This increased responsiveness of nociceptive neurons is referred to as peripheral sensitization.[8]

Both peripheral and central sensitization, clinically referred to as pain sensitization, can contribute to painful knee OA. Pain sensitization may be useful as a clinical construct to alert clinicians to patients with a potentially upregulated nociceptive state and is proposed to contribute to an enhanced, persistent and more widespread pain response.[11] Recent studies in knee OA have found the presence of increased pain sensitivity at remote sites, enhanced temporal summation (TS) and hypersensitivity to various stimuli to be associated with reports of more severe symptoms.[5,6,12] However these cross-sectional studies linking features of sensitization to greater levels of pain and disability do not explore if pain sensitivity has any prognostic implications.

There is also some evidence to suggest increased pain sensitivity negatively affects treatment outcomes. In painful musculoskeletal conditions such as shoulder impingement and lateral epicondylalgia widespread pressure pain sensitivity and thermal hyperalgesia, have been linked with a poorer prognosis.[13,14] Surgical outcomes for knee osteoarthritis may also be affected, with the presence of increased pain sensitivity prior to total knee replacement associated with more persistent pain after surgery.[15,16]

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4 Although joint replacement is considered an effective treatment for end-stage knee
5 OA, the majority of patients are managed conservatively. Physiotherapy is the widely
6 recommended conservative treatment approach for knee OA.[17] Existing studies of
7 prognosis in knee OA have focused on demographic and psychological
8 variables.[18–20] Whilst it has been suggested that central pain processing may
9 contribute significantly to the clinical pain experience in some people with knee
10 OA[21], no longitudinal studies have explored the potentially negative prognostic
11 impact of pain sensitization on outcomes in response to physiotherapy. In whiplash
12 associated disorders the presence of sensory hypersensitivity and cold hyperalgesia
13 has been shown to reduce the likelihood of a positive response to physiotherapy
14 treatment.[22] Thus it is conceivable, but currently unproven, that knee OA patients
15 with evidence of pain sensitization have poorer outcomes following physiotherapy.
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19 One obstacle to investigating the implications of pain sensitization is reliably
20 identifying it in the clinical setting. Due to the complexity of pain mechanisms it is
21 inadvisable to rely on any single test to reflect peripheral and central pain
22 mechanisms.[23,24] A multi-tissue assessment using a multi-modal stimuli approach
23 has been advocated,[25], and will be adopted in this study. The association between
24 key features of pain sensitization and clinical characteristics in knee OA have been
25 previously investigated. Our study will be the first to prospectively explore the effect
26 of key features of pain sensitization on physiotherapy outcomes in knee OA.
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30 This study will investigate the extent to which pain sensitization predicts non-
31 response to physiotherapy in patients with knee OA. Identifying clinical and
32 psychophysical features of pain sensitization in knee OA predictive of a poor
33 response to physiotherapy might help inform the management of such patients. It
34 may encourage clinicians to consider additional or alternative interventions aimed at
35 reducing such pain sensitization and optimise outcomes.
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38 **Study aims**

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40 The main aims of the study are; firstly to provide a comprehensive description of the
41 somatosensory characteristics of people with pain associated with knee OA (by
42 means of quantitative sensory testing (QST), and validated questionnaires
43 measuring pain, functional capacity and quality of life) and secondly, to investigate if
44 the presence of pain sensitization at baseline is predictive of non-response to
45 physiotherapy treatment as defined by treatment responder criteria.
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We hypothesise that the presence of pain sensitization will predict a non-response to physiotherapy treatment compared to patients without evidence of pain sensitization.

METHODS AND ANALYSIS

Study design

A multi-centre observational cohort study with assessments at baseline, post-treatment and at six months will be conducted. Following the baseline assessment for features of pain sensitization all participants will receive usual physiotherapy care. The relationship between pain sensitization and outcomes in terms of pain and disability will be explored through regression analysis.

Setting

The study will be undertaken in the physiotherapy outpatient departments of three large publicly funded university teaching hospitals in Dublin, Ireland.

Participants

Patients with symptomatic knee OA referred for physiotherapy treatment by a hospital consultant or clinical specialist physiotherapist will be eligible for inclusion. Full details of inclusion/exclusion criteria are summarised in Table 1.

At the time of recruitment knee pain must be the participant's primary musculoskeletal complaint for which they are seeking treatment, and physiotherapy must be the main treatment being undertaken over the study period. Participants recruited at physiotherapy led musculoskeletal assessment clinics will be screened for eligibility by the clinical specialist physiotherapist. The principal investigator will screen patients on the physiotherapy waiting list over the telephone.

Table 1. Study inclusion and exclusion criteria

Inclusion Criteria	
Diagnosis	Knee osteoarthritis based on American College of Rheumatology clinical criteria [26] and confirmed by radiographic findings
Age	Over 50 years
Pain duration	Knee pain for at least 6 months
Severity	Average pain over past week rated as moderate or severe by the patient
Medication	Willing to abstain from simple analgesics, NSAIDs, weak opioids or

	medications that combine these, for 24 hours prior to testing
Consent	Willing and able to give full consent
Exclusion Criteria	
Pathology	Lumbar or cervical radiculopathy, systematic inflammatory disease, positive screen for diabetic neuropathy, neuropathic pain
Past medical history	Previous surgery or disease of the peripheral or central nervous system, sensory loss secondary to chemotherapy or radiotherapy, fibromyalgia, chronic fatigue syndrome
Cognitive ability	Cognitive or psychiatric disorder interfering with ability to fully consent or cooperate with assessment
Other treatment	Injection or physiotherapy treatment for knee joint within previous 3 months
Medication	Taking anti-depressant or anti-convulsant medication, strong opioids

Healthy controls

Healthy participants are defined as people with no current pain or chronic pain problems in the past year. Forty age and gender matched controls will be recruited. Controls aged 50 to 65 years will be recruited mainly from the staff and student population of University College Dublin while pain-free controls aged 65 to 80+ years will be recruited from the general population. Recruitment will be purposive in order to fill the quotas in terms of age and gender. The controls will provide reference data for QST results.

Investigator

The principal investigator, (HOL) collecting all baseline and follow-up data, will be a senior physiotherapist with twelve years clinical experience. The same investigator will carryout all tests and is trained in using QST.

Recruitment procedure

A consecutive sample of knee OA patients with moderate/severe knee pain will be recruited. Between October 2014 and September 2015 potentially eligible participants will be identified at musculoskeletal assessment clinics and from physiotherapy outpatient waiting lists. A feasible recruitment rate is estimated at 12 patients per month with recruitment continuing until the specified numbers are achieved. Potential participants will be screened over the telephone and asked to choose a categorical pain descriptor (mild/moderate/severe). Patients who rate their symptoms as mild (average symptoms over the past week) will be excluded. Those

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3 who meet the other inclusion criteria will be asked to attend for an assessment prior
4 to commencing physiotherapy treatment. Written informed consent will be obtained
5 before enrolment in the study. Figure 1 represents the flow of participants through
6 the study.
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10 **Physiotherapy management**

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12 Physiotherapy treatment will be in line with current clinical guidelines for the
13 management of knee OA.[27] Treatment will typically involve between four and six
14 physiotherapy appointments. In some cases treatment may take the format of a small
15 group exercise intervention. A workshop led by the principal investigator will be held
16 at each recruitment site prior to study commencement where physiotherapists will
17 receive an update on clinical guidelines and current best evidence on management
18 of knee OA. This will standardise treatment to some degree, but intervention will be
19 individualised at the discretion of the treating physiotherapist and in consultation with
20 the patient.
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27 **Assessment**

28 **Baseline assessment**

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30 A schematic view of the outcome measures recorded at baseline and follow up is
31 presented in Table 2. Each assessment will take approximately one hour to
32 complete. Some questionnaires will be posted and completed in advance by
33 participants.
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37 **Follow up assessment**

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39 The primary endpoint will be at completion of physiotherapy treatment, this time point
40 is estimated to be on average at 3 months. Physiotherapy administration staff will
41 alert the principal investigator when a participant is discharged. Thereupon pain,
42 disability and global rating of change will be assessed by means of a postal
43 questionnaire. Information will also be recorded on use of co-interventions or any
44 change in medication for knee pain. This follow-up questionnaire will be administered
45 1 week of discharge from physiotherapy.
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51 Six months after enrolment into the study, participants will complete a postal
52 questionnaire assessing pain and function. They will exit the study at this point.
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55 **Assessment procedures and minimising bias**

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57 Studies support the reliability of QST measures where protocols are standardised
58 and both the tester and participant are carefully instructed.[25] Standardised
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assessment procedures will be followed in this study. At each location testing will be undertaken in the same temperature controlled room by the same investigator, using a single set of testing devices. Each session will begin by familiarising participants with standardised test procedures.[28,29] Physical testing will be performed by the investigator prior to in-depth subjective assessment or without knowledge of questionnaire scores. Test order is important,[30], and a pre-determined sequence will be used beginning with non-noxious stimuli. CPM can induce a residual effect and will be the final test.[31] With bilateral symptoms the most painful knee will be selected, if both are equally symptomatic the right knee will be tested. Where shoulder pain is present unilaterally the opposite forearm will be used for testing.

Table 2. Outcome measures and collection points

Domain	Variable	Instrument for Data Collection	Collection Points
Demographics	Age, Gender, Educational attainment, Employment status, Marital status	Baseline assessment questionnaire	Baseline
Pain	Self reported pain	WOMAC pain sub-scale	Baseline, post treatment*, 6 months
	Pain intensity	Numerical rating scale	Baseline, 6 months
	Location & quality	Knee Pain Map	Baseline
	Neuropathic pain symptoms	Modified PainDETECT	Baseline
	Characteristics of osteoarthritic pain	Intermittent and Constant Osteoarthritis Pain Instrument	Baseline
	Widespread pain	Body chart Manual tender point count	Baseline
Function	Self reported function	WOMAC function sub-scale	Baseline, post treatment, 6 months
Quality of life	Health related quality of life	EQ-5D 5L	Baseline
Central Sensitization Symptoms	Non-musculoskeletal central sensitization symptoms	Central Sensitization Inventory	Baseline
Quantitative Sensory Testing	Light touch	Von Frey filaments	Baseline
	Vibration	Graded tuning fork	Baseline
	Pain pressure thresholds	Pressure algometry	Baseline
	Dynamic allodynia	Brush stroke	Baseline
	Static allodynia	Von Frey Filaments	

	Thermal hyperalgesia	Thermo-rollers	Baseline
	Temporal summation	Repetitive mechanical stimuli with weighted pinprick	Baseline
	Conditioned pain modulation	Cold pressor test (conditioning stimulus) and PPTs (test stimulus)	Baseline
Confounding Variables	Obesity	Ratio of waist circumference to height	Baseline
	Depressive symptoms	Centre for Epidemiologic Studies Depression Scale	Baseline
	Comorbidities	Self Administered Comorbidity Questionnaire	Baseline
Management related variables	Treatment adherence	Sports Injury Rehabilitation Adherence Scale	During treatment
		Patient attendance ratio	During treatment
		Home Exercise Compliance Assessment	During treatment
	Treatment type and duration, Adverse effects	Therapist record sheet	During treatment
	Medication use and co-Interventions	Follow-up questionnaire	Post treatment, 6 months
Treatment outcome	Response to treatment	OARSI Responder Criteria; WOMAC pain and function subscales, global rating of change	Post treatment

* Post treatment assessment will be at approximately 3 months

Primary outcome variable

The main outcome is response to physiotherapy treatment and this will be determined using a set of responder criteria by the Outcome Measures in Rheumatology - Osteoarthritis Research Society International (OMERACT-OARSI).[32] Non-response to physiotherapy will be the designated categorical dependent variable upon which the subsequent regression analyses will be based.

The responder criteria will be applied to the relevant data gathered at post treatment follow-up and are summarised in Figure 2. For application of these criteria pain and function will be measured with the subscales of the Western Ontario and McMasters University Score Osteoarthritis Index (WOMAC LK 3.0). Validity and reliability of these subscales are well established, including for postal surveys.[33–35] Global rating of change will be measured with a 7-point Likert scale. This scale captures relevant change by asking the patient about any improvement or deterioration that

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3 has occurred with physiotherapy treatment.[36] Two points on the scale represents a
4 20% improvement.
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7 **Secondary outcome variables**

9 **Pain assessment**

10 The following valid and reliable measures of pain will be recorded; The Pain Intensity
11 Numerical Rating Scale (Pain NRS) will measure participant's average pain intensity
12 over the previous seven days.[37,38] The Knee Pain Map will be used to record
13 more detailed information about the location and quality of knee pain.[39]
14 Widespread pain is defined for this study according to the American College of
15 Rheumatology classification criteria using pain drawings marked by participants on a
16 body manikin.[40] Widespread pain is associated with more severe knee pain and
17 functional decline.[41,42]
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24 **Pain and quality of life questionnaires**

25 *Modified PainDETECT (mPD-Q)*

26 This questionnaire will record any neuropathic component to participants' symptoms.
27 It has been previously used for the screening of neuropathic pain-like symptoms in
28 knee OA in an elderly cohort.[43] Participants with more neuropathic pain-like
29 symptoms (scores > 12/38) are more likely to have signs of central sensitisation.[44]
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35 *Intermittent and Constant Osteoarthritis Pain Instrument (ICOAP)*

36 This validated questionnaire assesses various facets of both intermittent and
37 constant pain for the knee, including effects on sleep and quality of life, degree of
38 frustration and worry associated with the pain.[45] Two predictability items will be
39 administered to capture unpredictable spontaneous pain, thought to have the
40 greatest impact on participant well-being.[46]
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46 *Central Sensitization Inventory (CSI)*

47 This self-report inventory has preliminary validity and reliability and assesses for
48 symptoms not related to the musculoskeletal system but common to central
49 sensitization syndromes.[47,48] Good sensitivity (81%) and specificity (79%) values
50 were found with a cut-off score of 40 (out of 100) to identify patients with symptoms
51 of central sensitization.[48]
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56 *EuroQoL EQ-5D*

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3 The EQ-5D is a frequently used generic quality of life instrument, designed by the
4 EuroQoL group.[49] A modified form has been developed with an enlarged number
5 of possible answers to avoid a ceiling effect.[50] The EQ-5D has acceptable reliability
6 and validity when used in patients with knee OA.[51]
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10 11 **Quantitative Sensory Testing (QST)**

12 QST is a psychophysiological measure of perception in response to external stimuli
13 of controlled intensity.[29] This QST protocol will make reference to the well-
14 established German Neuropathic Pain Consortium (DFNS) protocol,[29], and will
15 utilise clinical QST methods recommended by the International Association for the
16 Study of Pain.[28] This current study's assessment protocol aims to be more
17 accessible using tools that are relatively inexpensive and adaptable to the clinical
18 setting.[52] Test sites used will be as follows; *Site 1*: On the medial or lateral knee
19 joint line, depending where the patient indicates their greatest pain (3 cm medial to
20 medial edge of patella or corresponding site laterally), *Site 2*: Over ipsilateral tibialis
21 anterior muscle (5 cm distal to the tibial tuberosity), *Site 3*: On the contralateral
22 forearm (5 cm distal to lateral epicondyle of humerus on the volar aspect).
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29 Somatosensory abnormalities over the area of *Site 2* tibialis anterior are thought to
30 provide evidence of spreading sensitization from the symptomatic knee. Changes at
31 *Site 3* could indicate more widespread sensitization at a generalised level in the
32 central nervous system,[11], although this can not be concluded definitively as other
33 explanations for abnormal QST results outside the knee are also possible, for
34 example patients with knee OA frequently have multi-site pain.[41]
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39 *Light touch*

40 Mechanical detection thresholds will be tested using a set of von Frey filaments
41 (Opti-hair2-Set, Marstock, Germany). Monofilaments beginning with the smallest
42 diameter will be applied to the skin. Light touch threshold (gm/mm^2) will be recorded
43 as the last filament (gm/mm^2) that can be perceived. Test-retest reliability of this
44 method for knee OA has been established.[53]
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49 *Mechanical allodynia*

50 Dynamic mechanical allodynia will be assessed by lightly stroking the knee and
51 forearm with a brush stroke three times (Senselab Brush No 5, Somedic). Static
52 allodynia will be assessed using von Frey filaments. The presence of mechanical
53 allodynia will be recorded if this non-noxious stimulation evokes a sensation of
54 pain.[54]
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Thermal hyperalgesia

Thermal rollers with predetermined temperatures of 25°C (cold) and 40°C (warm) (Senselab Rolltemp Somedic) will be used to detect thermal hyperalgesia at the forearm and knee.[52] Participants will be asked to report if the thermal sensation is perceived as painful when the rollers are passed lightly over the skin.

Vibration

Vibration detection threshold will be measured with a graded tuning fork (Rydel–Seiffer, 64 Hz) placed over 3 bony prominences (ulnar styloid, patella and medial malleolus). Vibration detection threshold is determined as a mean disappearance threshold of the vibrations on an 8/8 scale with the stimulus repeated three times.[29]

Pressure pain thresholds (PPTs)

Pressure will be applied using an electronic digital algometer with a probe size of 1 cm² (SomedicAB, Sweden) and an application rate of 30 kPa/s. The participant will be instructed to press an automatic cut off button when the first sensation of pressure pain is perceived. A cut-off point is set at 1000kPa. PPTs will be measured 3 times at the 3 test sites; the first measurement will be excluded and the mean of the last two measurements will be used for analysis. Test-retest reliability using this technique has been demonstrated in patients with knee OA.[55]

Mechanical temporal summation (TS)

The participant will assign a pain rating to a single stimulus by a weighted pinprick (MRC Systems 256 mN) and estimate an overall pain rating for a series of 10 pinprick stimuli of the same intensity (1/s applied within an area of 1 cm²).[29] This procedure will be applied twice on a marked area at the forearm and knee site. To get a value for TS the mean pain rating of the two pinprick trains will be calculated minus the mean pain rating of the two single stimuli will give a value for TS.[56]

Conditioned pain modulation (CPM)

The cold presser test is recommended for assessment of CPM in the clinical setting. [57,58] The test stimulus will be PPTs, while the conditioning stimulus will be cold immersion. PPTs will be recorded as outlined above. With the participant seated comfortably, the opposite arm to that used for PPT testing will be immersed in a bath of icy water (4°C monitored by thermometer) up to the elbow for 60 seconds. Participants unable to tolerate the water bath will rate their pain before withdrawing

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3 the arm (aim for at least 5 on NRS).[31,57] Re-testing of PPTs on the contralateral
4 forearm will take place immediately after immersion. The PPT values after the cold
5 pressor test will be divided by PPTs recorded before the test. A value of ≤ 1 will be
6 taken to reflect no CPM effect.
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9 10 11 **Manual tender point examination**

12 Tender points are typically identified according to the American College of
13 Rheumatology criteria for fibromyalgia.[59] Points can be reliably identified by
14 application of pressure with the thumb pad of the tester's dominant hand to 18
15 designated sites for 4 seconds until 4 kg (450kPa) of pressure is achieved. Those
16 points where pressure causes pain are summed to give a tender point total.
17
18 Detecting tender points with digital palpation has good intra-rater reliability and is
19 considered a useful clinical measure for deep tissue hyperalgesia.[60]
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24 25 **Patient adherence**

26 Patient adherence to treatment is thought to be an important determinant of clinical
27 outcome in knee OA.[17,61] The physiotherapist will calculate an attendance ratio for
28 each patient.[62,63] Additionally The Sports Injury Rehabilitation Adherence Scale
29 (SIRAS) will be used to measure physiotherapists' perceptions of their patient's
30 rehabilitation adherence at each clinic appointment. In addition to its proven
31 psychometric properties, the SIRAS has been shown to be a reliable scale for use in
32 clinical physiotherapy.[64] The Home Exercise Compliance Assessment (HECA) is a
33 widely used self-report method of assessment to measure adherence. At each
34 physiotherapy appointment participants will record the extent to which they adhered
35 to home exercises and physical activity advice since their previous clinic
36 appointment.[63]
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44 45 **Confounding variables**

46 Potentially confounding socio-demographic parameters, including age, gender,
47 marital status, employment status and educational level will be recorded on a
48 standardized form.[20,65,66] Obesity will be measured by recording participants'
49 waist circumference to height ratio.[67]
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53 Other factors known to predict poor outcome in knee OA or influence pain and
54 disability will be accounted for including multiple comorbidities and depressive
55 symptoms.[18] The Centre for Epidemiologic Studies Depression Scale (CES-D) is a
56 valid and reliable measure of depression in community dwelling elderly and a score
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3 >16 is considered indicative of depressive symptoms.[68] For each of these variables
4 the method of assessment is detailed in Table 2.
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8 The presence of widespread pain is another potential confounder,[41] however it
9 could also be a mediator between pain sensitization and QST measures such as
10 lowered PPTs remotely. For this reason the regression model will not be adjusted for
11 this variable.
12

13 Radiographic severity of knee OA is poorly correlated with self-reported pain and
14 pain sensitization. [5,6] For these reasons x-ray results will not be included in the
15 analysis.[69]
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18 **Data Analysis Plan**

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20 In order to describe the somatosensory characteristics z-scores will be calculated for
21 individual OA patients. The control group will provide reference data for QST results
22 and enable calculation of a standardised z-score using the following formula:
23

24
$$z = (\text{value}_{\text{participant}} - \text{mean}_{\text{controls}}) / \text{standard deviation}_{\text{controls}}$$
 [29] Calculating the z-score
25 for each QST modality and body site facilitates the comparison of QST results with
26 healthy control subjects independent of the unit of measure. For data analysis where
27 cut-off points are required z-scores outside the 10th and 90th percentile (or 1.28
28 standard deviations of the mean) will be classified as abnormal.
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34 To address the first aim descriptive statistics will be calculated for all outcome
35 measures at baseline, including for all continuous variables, means, standard
36 deviations, or medians with ranges of scores; and for categorical variables,
37 frequencies and percentages. In summarising descriptive QST data, z-score
38 calculations and cut-off points will determine the prevalence of somatosensory
39 abnormalities in pressure pain thresholds, mechanical detection threshold, and
40 vibration threshold. Somatosensory abnormalities such as allodynia or cold
41 hyperalgesia will be classified as either present or absent.
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48 Initial analyses for the second aim will be exploratory to compare symptom profiles
49 between people who respond to treatment and treatment non-responders. These will
50 be categorised by the OMERACT-OARSI responder criteria as described previously.
51 Categorical variables will be analysed using chi-square tests. Multivariate analysis of
52 variance (MANOVA) will be used to compare continuous normally distributed
53 variables between responders and non-responders, and from this variables
54 associated with responder status will be identified. The Mann Whitney test will be
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3 used for comparison of variables that are not normally distributed. In cases where
4 data is missing multiple imputations will be applied. A sensitivity analysis will be
5 carried out to assess if this changes the results.
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9 A principal component analysis (PCA) will be used to determine which variables
10 relating to sensitization (light touch, vibration, allodynia, cold hyperalgesia, PPT arm,
11 PPT knee, PPT tibia, TS arm, TS knee, CPM) to include in the predictive model.[70]
12 PCA may facilitate data reduction as some variables related to pain sensitization may
13 be highly correlated while some sensory modalities may represent distinct individual
14 dimensions of pain perception.[71] Prior to conducting PCA the suitability of the data
15 for this type of analysis will need to be assessed. Components with an eigenvalue >
16 1.0 from PCA will be subsequently entered into the regression model investigating
17 predictive factors for non-response to physiotherapy.
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21 A logistic regression model will be developed to predict non-response to
22 physiotherapy treatment with 'treatment non-responder' (yes/no) as the dependant
23 variable. Variables will be chosen for inclusion in the first model iteration if they are
24 found to be associated with non-responder status in uni-variate analysis with a
25 threshold of $p < 0.05$, or if their inclusion is supported by previous literature. The
26 model will be adjusted for predetermined variables such as age, gender,
27 socioeconomic status, depressive symptoms, treatment adherence and
28 comorbidities.[18,20,65,66] Results of the principal component analysis will be
29 entered into the regression model. It is anticipated that the regression model will
30 accommodate a maximum of 7 variables with statistical significance accepted if
31 $p < 0.05$. The best fitting and most parsimonious model will be selected as the final
32 iteration and cross validation of the predictive model will be performed.[72] A
33 secondary sub-analysis will explore the ability of some individual QST modalities to
34 predict non-response to physiotherapy if entered into the regression model as single
35 variables.
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38 Data will be analysed using SPSS v 20 (SPSS Inc., Chicago, IL) and R v 3.0.2.
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46 47 48 49 **Sample size**

50 The sample size is calculated based on the number of anticipated explanatory
51 variables planned for inclusion in the logistic regression model. It is expected that a
52 maximum of 7 explanatory variables will be included and 10 cases i.e. non-
53 responders will be allowed for each explanatory variable.[73] It is estimated that 60%
54 of patients will be classified as non-responders to physiotherapy by the OMERACT-
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OARSI criteria.[74] Recruiting 140 participants while allowing for a 15% loss to follow-up should ensure adequate numbers.

Dropouts

All participants will be followed up on discharge from physiotherapy. Patients who discontinued treatment will have the opportunity to provide follow-up data. Patients will be considered lost to follow-up if they do not complete the primary outcome measure post treatment.

ETHICS AND DISSEMINATION

This study has been approved by St. James's Hospital/AMNCH Research Ethics Committee (ref. no. 2013/11/Chair) and by the St. Vincent's Healthcare Group Ethics and Medical Research Committee (ref. no. HOL/9414) and will be conducted in accordance with the Helsinki Declaration. Fully informed written consent will be obtained and patients incapable of giving full consent will not be recruited.

The study findings will be presented at national and international conferences and will be published in peer-reviewed journals.

DISCUSSION

To our knowledge this is the first study to examine the effects of pain sensitization on clinical outcomes in response to physiotherapy in patients with knee OA. The research is exploratory in nature and some limitations are outlined below. For the purposes of this clinical research the term pain sensitization will be utilised however the lack of a widely accepted definition and criteria for identifying pain sensitization is acknowledged as a limitation.

It is recognised that some experimental pain modalities such as enhanced TS and facilitatory CPM are often interpreted as hallmarks of pain sensitization but these can also occur in healthy populations.[56,58] It is important to acknowledge ~~due to~~ this natural variability in responses and the likelihood of these tests capturing false positives. To account for this no individual QST modality will be used as a stand-alone measure of pain sensitization and QST results will be compared to normative data.

The QST protocols originally developed for assessing neuropathic pain are lengthy.[29] However if somatosensory testing is to be incorporated into routine clinical practice it must be both time and cost-efficient.[52,75] This study will focus on

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3 tests to identify features of pain sensitivity based on their utility and practicality in the
4 clinical setting. However these criteria necessitate the exclusion of certain tests, such
5 as thermal pain thresholds, that are difficult to carrying out reliably in the clinical
6 setting in a limited time frame.
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10 The central concern of this study relates to alterations in pain processing and any
11 potential relationship with poorer prognosis in knee OA. A range of clinical,
12 psychological and socio-demographic predictors of poor outcome have been
13 identified.[76–78] Incorporating all these variables is not feasible and would make for
14 an unacceptably long participant assessment and complex analytical model.
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16 Nonetheless the most important predictor variables will be accounted for in the
17 analysis.
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21 This clinically based observational study does not aim to investigate the effects of
22 specific physiotherapy treatments. It will observe people undergoing usual
23 physiotherapy and variation in the intervention is to be expected. Nonetheless an
24 attempt to standardise care to some degree will be made by using current evidence
25 based guidelines and keeping a record of the physiotherapy intervention and
26 adherence for each participant.
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31 Recruiting the participant sample from the secondary care setting will limit the ability
32 to generalise the study findings to patient populations in primary care. The
33 generalizability is further limited by only including patients with moderate or severe
34 knee symptoms. This limitation was deemed necessary in order to include sufficient
35 numbers of patients likely to have features of sensitization, as we know pain
36 sensitization is related to pain intensity.[5] Furthermore optimising management in
37 secondary care is a priority; this is where Irish patients usually access not just
38 physiotherapy services but more invasive treatments such as joint injection or
39 surgery.
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46 The analyses reported in this study will be exploratory and generate rather than
47 confirm hypotheses about pain sensitization and physiotherapy for knee OA. It is
48 acknowledged that widespread pain hypersensitivity and somatosensory
49 abnormalities can arise from a host of complex and interacting neurophysiological,
50 psychological and immunological processes.[21]
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54 Given its relatively short follow-up period we cannot infer causality directly from our
55 data with regard to pain sensitization and physiotherapy outcomes. Nonetheless it
56 may point to a relationship worthy of further investigation in order to better
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3 understand pain mechanisms in knee OA and optimise physiotherapy outcomes in
4 the future.
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8 FOOTNOTES

9
10 **Acknowledgements** We would like to acknowledge the Physiotherapy Departments
11 of St. James's Hospital, St. Vincent's University Hospital and Tallaght Hospital,
12 Dublin for agreeing to facilitate this research.

13 **Competing Interests** The authors declare that they have no competing interests.

14
15 **Funding** This work was supported by a Research Fellowship for Healthcare
16 Professionals from the Health Research Board, Ireland. Grant number:
17 HPF/2013/449.
18

19
20 **Authors' Contributions** HOL, CD, KS and NM assisted with the protocol design.
21 CD, KS, NM and HOL procured the project funding. CB provided statistical advice.
22 All authors provided feedback on drafts of the paper and approved the final
23 manuscript.
24
25

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27 **Data sharing statement** It is the intention of the study group, that once the study is
28 completed, and the research articles arising from the study have been published, any
29 data that is fully anonymised and not sensitive would be made open access.
30 However because this intention was not declared in the original ethical applications
31 this action would be subject to approval by the relevant research ethics committees.
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18 **Figure Legends**

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21 **Figure 1** Flow of participants through the study
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24 **Figure 2** Set of responder criteria [32]
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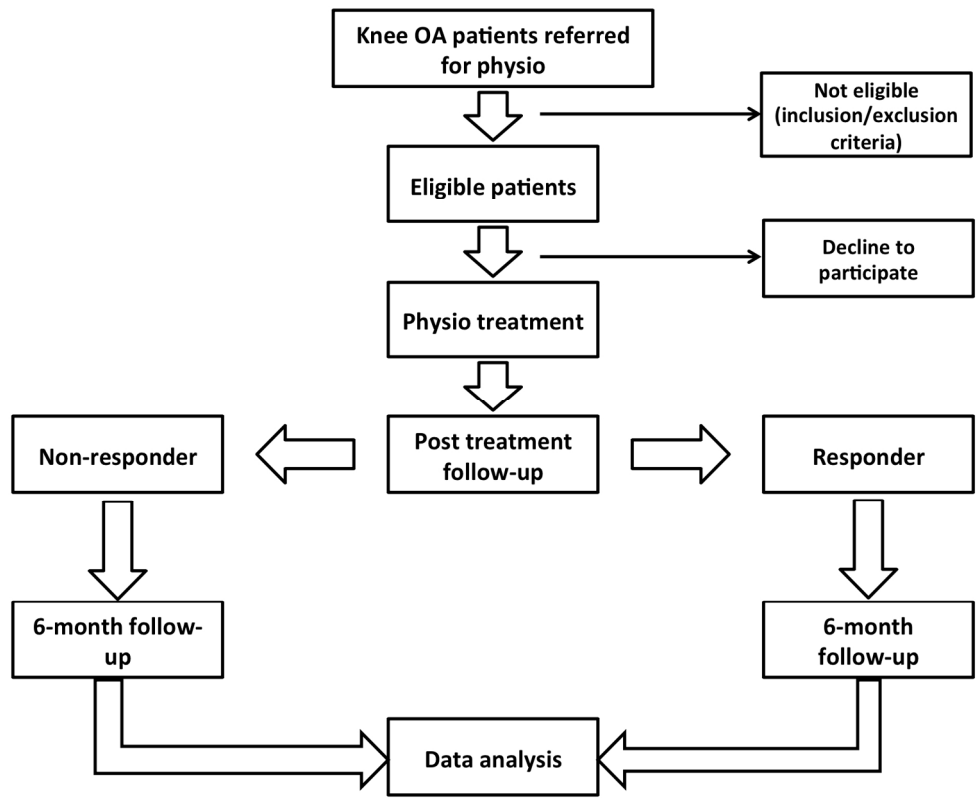


Figure 1 Flow of participants through the study

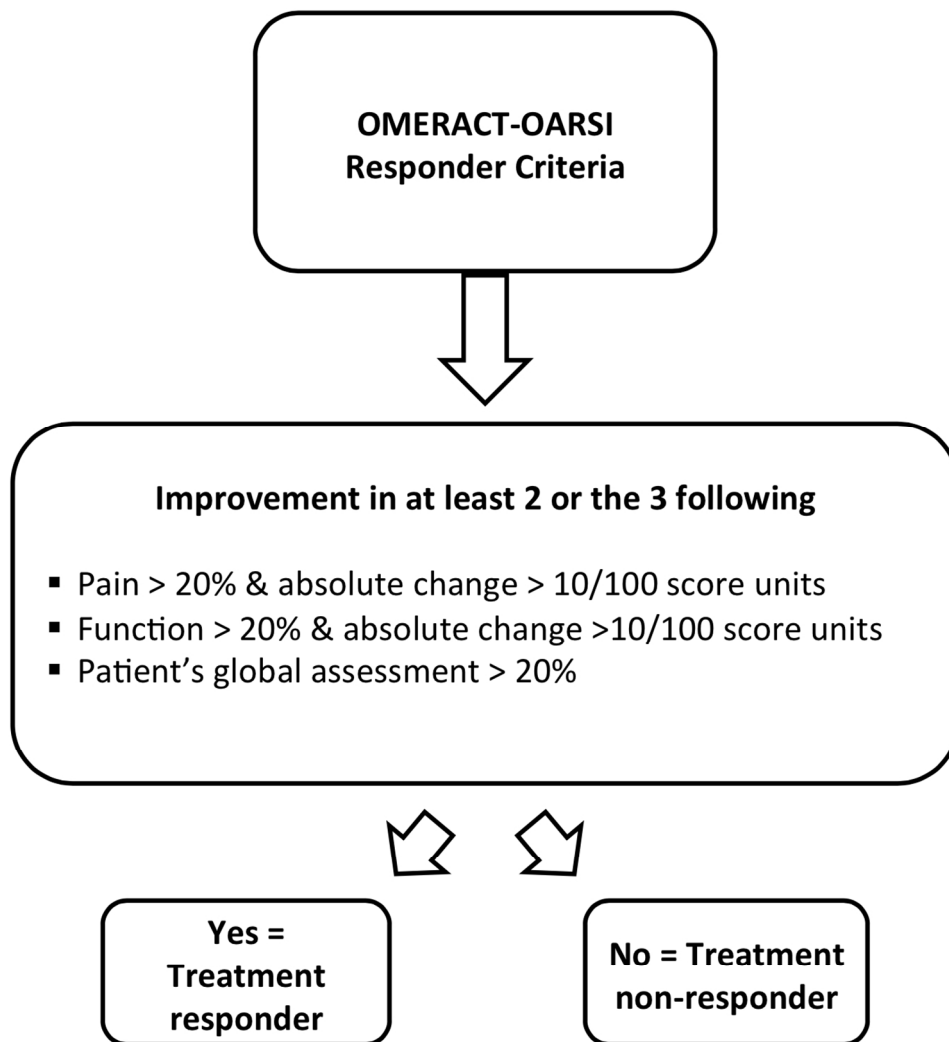


Figure 2 Set of treatment responder criteria [33]

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4 & 5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6 & 7
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9, 10, 11, 12, 13, 14
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Table 2, 10, 11, 12, 13, 14
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	16
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	15, 16
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	15, 16
		(b) Describe any methods used to examine subgroups and interactions	NA
		(c) Explain how missing data were addressed	16
		(d) If applicable, explain how loss to follow-up was addressed	17
		(e) Describe any sensitivity analyses	17
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations			17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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