PAIN PRESSURE THRESHOLDS AND PSYCHOSOCIAL CORRELATES IN PEOPLE WITH KNEE OSTEOARTHRITIS

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Thesis abstract

This thesis focusses on chronic pain, pain sensitivity, depression, and anxiety in people with knee osteoarthritis (OA). The thesis includes details of three interrelated sub-studies: *Study 1*: An investigation into the associations between pain pressure thresholds (PPTs) and self-reported pain, depression, anxiety, and gender in knee OA; *Study 2:* An investigation into the inter-rater reliability of pressure algometry Quantitative Sensory Testing (QST); and *Study 3:* Rasch analysis of the State-Trait Anxiety Inventory short form (STAI-SF).

Previous research into self-reported pain and pain sensitivity assessed *via* QST in knee OA suggests that there are significant associations between these factors and depression and anxiety. However, few studies have investigated the relationships between pain sensitivity and mood in people with knee OA, as the majority of these studies are very medical in their focus. Gender differences in some QST studies have also been found, with women often presenting with lower pain thresholds than men. However, this finding has not been consistent, and appears to vary across different samples.

For Study 1, 77 people with a diagnosis of knee OA completed self-report measures of current pain level, depression, and anxiety. PPTs at four body sites were then measured for each participant using QST. Correlations showed that female gender, higher pain rating, and higher levels of depression and anxiety, were associated with lower PPTs. Parallel multiple regression models found that self-reported pain rating, depression, anxiety, and gender explained between 13 and 18% of the variance in PPTs (for each individual body site).

For Study 2, 20 healthy participants underwent the QST procedure used in Study 1 to measure their PPTs at four body sites. The QST was administered by the two testers who administered the QST in Study 1, in order to investigate inter-rater reliability. Acceptable inter-class coefficients were found for each body site PPT, suggesting that lack of inter-rater reliability was not a weakness of Study 1.

For Study 3, 246 people with a diagnosis of knee OA completed the STAI-SF. In order to evaluate the measurement properties of the STAI-SF with this client group, Rasch analysis was undertaken. The study examined the fit between the data collected from the STAI-SF and the Rasch model, in order to investigate whether it meets the psychometric requirements of interval-level measurement. An acceptable fit to the Rasch model was found, although the measure showed evidence of mistargetting.

The main conclusions of this thesis research were that, for people with knee OA, depression, anxiety, gender, and pain rating are related to PPTs and explain some of the variance in PPTs. The utility of the STAI-SF with people with knee OA was also queried. The key implication of this research is that it is important for the appropriateness of assessment tools used in knee OA for mood and pain (in research and/or clinical practice) to be more critically considered than they are in most current literature. This would help ensure that the data collected is more meaningful and helpful in guiding interventions for this client group.

Acknowledgements

I would like to take the opportunity to acknowledge the support provided by all those associated with the Trent Doctorate of Clinical Psychology at the University of Nottingham and University of Lincoln. Special thanks go to my research supervisors, Dr Roshan das Nair and Dr Bryan Moreton, for all their encouragement, support, knowledge, and reading of previous drafts. I would also like to thank all those associated with the Arthritis Research UK Pain Centre at the University of Nottingham, including Professor Nadina Lincoln and Professor David Walsh. Many, many thanks go to Maggie Wheeler at the Pain Centre, for all of her patience, support, efficiency and humour, which has got me through the many hours of data collection we have both undertaken together.

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On a personal note, I would like to thank my friends and family for their support throughout this project. In particular, thank you to Clare, who has been more supportive and encouraging than I could have ever imagined: thank you for the coffee!

Statement of contribution

Systematic literature review

- Literature review design: Dr Roshan das Nair, Dr Bryan Moreton, Victoria Tew
- Literature search: Victoria Tew (with supervision from Dr Roshan das Nair and Dr Bryan Moreton)
- Write-up: Victoria Tew (with supervision from Dr Roshan das Nair and Dr Bryan Moreton)

Journal article and extended paper

Study 1: QST main study (reported in the Journal Article and Extended Paper sections 1.1, 2.1 and 3.1)

- Project design: Dr Roshan das Nair, Prof Michael Doherty, Prof Nadina Lincoln, Dr Bryan Moreton, Dr David Walsh, Prof Brigitte Scammell
- Applying for ethical approval: Dr Bryan Moreton
- Recruiting participants: Dr Bryan Moreton and Maggie Wheeler
- Data collection: Victoria Tew and Maggie Wheeler collected the QST data. The depression and anxiety questionnaire data was collected by Dr Bryan Moreton and Maggie Wheeler
- Scoring questionnaires: Dr Bryan Moreton and Maggie Wheeler
- Data entry: Dr Bryan Moreton and Maggie Wheeler. Data checked by Victoria Tew for accuracy by comparing the electronic data set to the initial record forms.
- Data analysis: Victoria Tew (with supervision from Dr Roshan das Nair and Dr Bryan Moreton)
- Write-up (including the review of literature): Victoria Tew (with supervision from Dr Roshan das Nair and Dr Bryan Moreton)

Study 2: QST inter-rater reliability study (reported in the Extended Paper sections 1.2, 2.2 and 3.2)

- Project design: Dr Roshan das Nair, Prof Nadina Lincoln, Dr Bryan Moreton, Victoria Tew, Maggie Wheeler
- Applying for ethical approval: Dr Bryan Moreton, with input on ethics application from Dr Roshan das Nair, Prof Nadina Lincoln, Victoria Tew, and Maggie Wheeler
- Recruiting participants: Dr Roshan das Nair, Victoria Tew, Maggie Wheeler,
- Data collection: Victoria Tew and Maggie Wheeler
- Data entry: Victoria Tew and Maggie Wheeler. Data checked by Victoria Tew for accuracy by comparing the electronic data set to the initial record forms.
- Data analysis: Victoria Tew (with supervision from Dr Roshan das Nair and Dr Bryan Moreton)
- Write-up (including the review of literature): Victoria Tew (with supervision from Dr Roshan das Nair and Dr Bryan Moreton)

Study 3: STAI-SF Rasch analysis study (reported in the Extended Paper sections 1.3, 2.3 and 3.3)

- Project design: Dr Roshan das Nair, Dr Bryan Moreton, Victoria Tew
- Applying for ethical approval: Dr Bryan Moreton
- Recruiting participants: Dr Bryan Moreton and Maggie Wheeler
- Data collection: Dr Bryan Moreton and Maggie Wheeler
- Scoring questionnaires: Dr Bryan Moreton and Maggie Wheeler
- Data entry: Dr Bryan Moreton and Maggie Wheeler
- Data analysis: Victoria Tew (with supervision from Dr Roshan das Nair and Dr Bryan Moreton)
- Write-up (including the review of literature): Victoria Tew (with supervision from Dr Roshan das Nair and Dr Bryan Moreton)

Table of contents

List of tables and figures

List of appendices

Literature review

The effectiveness of psychological interventions for patients with osteoarthritis in reducing anxiety (Review)

Tew V, das Nair R, Moreton B

This review is written for submission to The Cochrane Library as a Cochrane intervention review. The guidelines for authors are available at: www.cochrane-handbook.org.

This review was undertaken by the lead author (VT) using the Cochrane Review Manager software version 5.1 (RevMan 2011). However, for this submission the review has been formatted in Microsoft Word so is not fully formatted according to Cochrane guidelines. Data synthesis is not included in this submission; however, meta-analysis will be included in the review submitted to The Cochrane Library.

[Intervention Review]

The effectiveness of psychological interventions for patients with osteoarthritis in reducing anxiety

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Dates

Assessed as up-to-date: 01 August 2012
Date of search: 01 August 2012

ABSTRACT

Background

Anxiety is often experienced by individuals with osteoarthritis (OA), and may affect the amount of pain experienced as well as the progression of the disorder. There is evidence that psychological interventions may be effective at reducing anxiety in OA patients. However, no systematic review has investigated this to date.

Objectives

To determine the effectiveness of psychological interventions at reducing anxiety levels in patients with OA.

Search methods

The following databases were searched: MEDLINE (Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R); 1966 to 1 August 2012); EMBASE (1980 to 1 August 2012); PsycINFO (1806 to July week 4 2012); and AMED (1985 to 1 August 2012). The reference lists of relevant studies, reviews and guidelines were also hand-searched.

Selection criteria

We selected randomised controlled trials (RCTs) or non-randomised controlled clinical trials (CCTs) of psychological interventions or interventions including a psychological component for patients with OA. Studies were only included if they assessed anxiety pre- and post- intervention. The trials selected had to include at least 1 intervention group compared to a control group or at least 2 intervention groups if there was no control group. Studies that included participants without OA were excluded unless separate data for the OA group was accessible.

Data collection and analysis

We assessed the quality and undertook data extraction for the selected studies. Guidelines outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011] were adhered to.

Results

Six studies, including 1293 participants with OA, were included. Most of the interventions were mixed multidisciplinary interventions which included a psychological intervention component, and most were delivered in a group format. Most of the psychological interventions were based on cognitive behavioural theory. The risk of bias was assessed as low for most of the included studies: only one of the studies was assessed as having a high risk of bias for any of the bias criteria. Only 2 studies reported significant reductions in anxiety post-intervention in the treatment group compared to controls. Two further studies, including three psychological interventions, reported significant reductions in anxiety post-intervention, but control data was either not collected or was not significantly different to intervention data.

Authors' conclusions

There is some evidence to support the use of psychological treatments to reduce anxiety in people with OA. However, most of the interventions in the included studies were mixed interventions, and so it is not possible to fully assess the impact of the psychological intervention: further research of stand-alone psychological interventions in OA is required. Furthermore, due to the low number and the poor methodological quality of the included studies, further high quality research trials are needed.

PLAIN LANGUAGE SUMMARY

Psychological interventions in Osteoarthritis and their effect on anxiety

People with osteoarthritis often experience anxiety, stress and worry. This anxiety can be linked directly to fears about their condition or a more generalised anxiety. Anxiety can lead to people using unhelpful strategies to manage their osteoarthritis, which can lead to their condition worsening. Anxiety might also have a direct effect on the worsening of the condition *via* the effects of stress on the body. Psychological treatments are offered to patients with osteoarthritis to help them manage the disorder and the effects that it has on their lives. There are currently a low number of studies which have investigated the effect of psychological treatment on reducing anxiety in people with osteoarthritis. This review included 6 studies with 1293 participants with osteoarthritis. These studies included psychological interventions or mixed treatments which included a psychological component. The results of this review found some evidence for the use of psychological interventions to reduce anxiety in people with osteoarthritis. However, this conclusion needs to be taken with caution because most of the interventions included other types treatment as well as psychological treatments. Also, the studies reviewed here were of limited quality. The review showed that more better-quality studies are needed to investigate the effect of psychological treatments on anxiety in people with osteoarthritis.

BACKGROUND

Description of the condition

Osteoarthritis (OA) is the most common form of arthritis in the UK, affecting an estimated 8.5 million people (Arthritis Care 2004). OA is characterised by tissue damage and abnormal bone growth at the affected body site (Arden 2006). The body sites most commonly affected by OA are the knee, hip, hand and spine (Arden 2006).

Pain is a common and chronic symptom in individuals diagnosed with OA (Arden 2006). Pain in OA has also been found to be associated with reduced physical and psychological health (Bookwala 2003). Psychological difficulties of depression and anxiety have been found to be highly prevalent in OA samples (Tallon 2000). Depression and anxiety have also been found to be viewed as a central problem in OA by OA patients (Tallon 2000).

The impact of depression on OA patients has been extensively investigated (e.g. Sale 2008). Anxiety in OA, however, has been investigated less extensively, despite being found to have similar prevalence when compared to depression in OA (McWilliams 2004; Riddle 2010). The link between OA and anxiety can be explained using the fear-avoidance model of chronic pain (Lethem 1983). The fear-avoidance model is a cognitive behavioural model which suggests that pain (e.g. due to OA) leads to anxiety if the individual appraises the pain in a catastrophizing manner. Lethem 1983 propose that individuals experiencing pain-related anxiety use avoidance strategies (such as reducing activity levels) as an attempt to reduce the anxiety experienced. According to this model, avoidance can then lead to disability and depression, which maintains, and can even increase, the pain experienced. Similarly, McWilliams 2004 suggest that anxiety difficulties may lead to increased maladaptive reactions to the physical symptoms of OA and to worsening of OA pathology.

Description of the intervention

Psychological interventions for OA patients are treatments based on psychological theory in which patients learn strategies to manage the physical, cognitive, behavioural and emotional impact of the disorder (Gay 2002). Psychological treatments for OA often include psychoeducation and discussions about pain and physical disability, as well as interventions focussed on reducing depression and anxiety (Gay 2002). Common psychological therapies in OA are Cognitive Behavioural Therapy (CBT) and Acceptance and Commitment Therapy (ACT) (Wetherell 2011).

Psychological interventions in OA are also provided as part of multidisciplinary treatment programmes, such as arthritis self-management programmes (Barlow 1998). Arthritis self-management programmes are usually more educational than pure psychological treatments (Gay 2002), with this education covering exercise and medication in addition to psychological factors such as anxiety (Barlow 1998). Self-management programmes are typically based on cognitive behavioural theory (Barlow 1998).

How the intervention might work

No firm explanations have been agreed for how psychological interventions in OA might work in relation to reducing anxiety, however several explanations have been proposed. Psychological interventions in OA might reduce anxiety levels as patients learn psychological strategies to cope with pain and other physiological symptoms of OA. These psychological strategies can give patients a sense of control over their symptoms, which can lead to reduced stress and anxiety (Williams 2007). Psychological strategies such as relaxation and mindfulness may also have a direct effect on reducing anxiety symptoms (Williams 2007).

Psychological interventions in OA often include psychoeducation about OA and its effects on physiology, thoughts, emotions and behaviour (Williams 2007), which might also have a direct effect on reducing fear and anxiety. Alternatively, psychological treatments in which patients learn additional strategies to cope with

OA pain could be effective at reducing anxiety as, according to the fear-avoidance model (Lethem 1983), reduced pain can lead to reduced catastrophizing beliefs, which can in turn lead to less pain-related anxiety.

Why it is important to do this review

Anxiety has been found to be a significant difficulty experienced in OA patients (Tallon 2000). It is therefore important to be aware of the effectiveness of psychological interventions in reducing anxiety in this patient group. Clarke 2009 undertook a review of systematic literature reviews focussed on the relationship between depression, anxiety and chronic diseases and associated interventions. This review found that systematic reviews of psychological interventions for anxiety had been conducted for rheumatoid arthritis samples but not OA samples. Clarke 2009 also found systematic reviews of the effectiveness of psychological interventions for depression in OA. This suggests that there is a gap in the literature regarding reviews focussed on the effectiveness of psychological interventions in OA on reducing anxiety.

OBJECTIVES

The aims of this systematic review are to determine whether:

1. Patients with OA who have received a psychological intervention show better outcomes in anxiety severity than those given no treatment or a control intervention and

2. Patients with OA who have received a mixed multidisciplinary intervention which includes a psychological element show better outcomes in anxiety severity than those given no treatment or a control intervention.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and Clinical Controlled Trials (CCTs) with patients with OA were sought for inclusion in the review if they met the following criteria:

1. A psychological intervention is compared to a control
2. Anxiety is assessed pre and post intervention using a scale outcome measure.

Types of participants

Trials included in the review were limited to those with OA patients, who may or may not have comorbid diagnoses. Multiple health difficulties are common in individuals with OA (Hopman-Rock 1997): therefore it is important to not exclude studies which include OA patients with additional diagnoses, to ensure that the review is ecologically valid. Trials will be included in the review if they include OA patients as part of the sample along with patients will other diagnoses if it is possible to access the data for the OA sample only. In such cases, the study authors will be contacted to provide this information if the OA only data is not published.

Types of interventions

Trials will be included if there is a comparison between a treatment group that received a psychological intervention and a control group that received either a different intervention or no intervention. Psychological interventions will be defined as a treatment of any length which is based on psychological theory. This will include psychological interventions delivered by non-psychologists, psychoeducational interventions, or psychological self-help. Trials will also be included if they investigate the effectiveness of a mixed multidisciplinary

intervention which includes a psychological component, such as an arthritis self-management programme.

Type of outcome measures

Primary outcomes

Primary outcomes were measures of anxiety, including measures of specific types of anxiety (e.g. fear of movement) or of anxiety more generally. Trials were included if anxiety was assessed using a scale outcome measure.

Secondary outcomes

No secondary outcomes were investigated in this review as the focus is purely on the effect of psychological interventions on anxiety.

Search methods for identification of studies

The following databases were searched and studies were identified by one reviewer (VT).

Electronic searches

We searched the following electronic databases:

1. MEDLINE (Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R); 1966 to 1 August 2012)
2. PsycINFO (Ovid; 1806 to July week 4 2012)
3. EMBASE (1980 to 1 August 2012)
4. AMED (1985 to 1 August 2012).

The MEDLINE (Ovid) search strategy (Appendix 1) was adapted for use with the other electronic databases.

Searching other resources

Additional studies were identified through hand-searching the reference list of relevant studies, reviews, and guidelines.

Data collection and analysis

Selection of studies

One review author (VT) developed the search strategy by consulting search strategies from relevant previously published reviews (Miles 2011; Suokas 2012; Veehof 2011; Wallis 2011; Yohannes 2010). The strategy was then reviewed by two other review authors (RdN and BM).

Abstracts of the studies identified using this search strategy were then evaluated by one author (VT) using the four inclusion criteria (see previous sections: types of trials, participants, interventions, and outcome measures).

Data extraction and management

One reviewer (VT) assessed the methodological quality of the included studies and rated them using Cochrane Collaboration Guidelines. A data extraction tool based on das Nair 2007 and CONSORT guidelines (Moher 2001) was used. As no CCTs were included in this review after study selection, this data extraction tool was appropriate for the studies identified. The data extraction tool would have been adapted for use with non-randomised controlled trials, using best practice suggestions (Deeks 2003). The following information was recorded for each study:

Method of participant assignment:

- Unit of assignment
- Method used to generate the intervention assignment schedule

- Method used to conceal the intervention assignment schedule from participants and clinicians until recruitment was complete
- The auditable process of executing the assignment method

Blinding:

- Whether (and how) outcome assessors were aware of the intervention allocation
- Whether the data analyst was aware of the intervention allocation
- Whether individual participant data were entered into the trial database without awareness of intervention allocation

Participant follow-up:

- The numbers and flow of participants, by intervention group, throughout the trial
- The average duration of the trial
- The reason for dropout clearly recorded
- The timing of the outcome measures

Statistical analysis:

- Whether the analysis used the intention-to-treat (ITT) principle
- The intended sample size and its justification
- Trial dropouts and completers
- The reliability, validity, and standardisation of the anxiety outcome measure(s)

Results:

- The appropriate analytical techniques applied to the anxiety outcome measure(s)
- The appropriate measures of variability (e.g. confidence intervals for anxiety outcome measures)
- The actual probability value and the nature of the significance test

Other characteristics:

- Sample size
- Age range/mean
- Type of OA
- Type of treatment, including modality (group or individual) and whether pure psychological treatment or mixed intervention
- Treatment duration
- Duration of follow-up
- Anxiety outcome measure(s) used

We conducted the review using the Cochrane Review Manager software version 5.1 (RevMan 2011).

Assessment of risk of bias in included studies

One review author (VT) assessed the risk of bias of the included studies and completed the 'Risk of Bias Table' as described in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (Higgins 2011). The table includes the following sections:

- Random sequence generation
- Allocation concealment
- Blinding (of participants, administrators, and data analysts)
- Incomplete outcome data
- Selective reporting of outcomes
- Other sources of bias

These criteria were assessed as being at a low or high risk of bias, or unclear if sufficient information was not provided. The reviewer was not blinded to the details of the studies (such as author, journal or institution) due to the reviewer's role in undertaking and reporting this review. A summary of the overall risk of bias was produced.

Dealing with missing data

When data was missing or unclear from an article, the first author was contacted for further information. In the case of studies including a mixed sample of OA patients and patients with other conditions, the first author was contacted for further information regarding data pertaining to the OA sample only. When the anxiety data was collated with other psychological variables, the first author was contacted for information regarding the anxiety data. This particularly applied for studies using the Arthritis Impact Measurement Scales (AIMS; Meenan 1980), as the anxiety data are often reported as part of the 'psychological' scale (based on Kazis 1983).

RESULTS

Description of studies

Results of search

A total of 89 studies were identified using the search strategy (84 through the search of electronic databases and 5 through the additional hand-search of relevant papers). The titles and abstracts of these 89 studies were reviewed and full papers were accessed for those studies which appeared to meet the inclusion criteria. Studies were excluded if they met the following exclusion criteria:

1. Not an intervention study;
2. Does not include at least one psychological intervention (based on psychological theory) or one broader intervention including a psychological component;
3. Sample includes patients without an OA diagnosis or the OA data is not available through published materials or communication with the lead author;
4. No pre- and post-intervention anxiety data: anxiety is not assessed or the data are not available from the lead author;
5. Not an RCT or CCT.

Excluded studies

Eighty-three studies were excluded after the application of the above exclusion criteria. Sixty-six studies were excluded as they were not intervention studies. Six studies were excluded because they did not include a psychological treatment. Three studies were excluded because the sample included individuals without an OA diagnosis and the OA sample data were not published or accessible after contact with the lead authors. Eight studies were excluded because no pre- and post-intervention anxiety data were available: anxiety was not assessed at all in 1 study; 1 study only assessed anxiety pre-intervention; and the anxiety data were not able to be provided by the lead authors of the other 6 studies.

Included studies

Following the above exclusion process, 6 studies, including a total of 1293 participants, met the review's inclusion criteria (Buszewicz 2006; Giraudet-Le Quintrec 2003; Jessep 2009; Laborde 1983; Wetherell 2011; Williams 2011). See Table 1 for a summary of the 6 included studies, and Table 2 for further details related to the data quality and risk of bias criteria.

Table 1. Summary of the characteristics of the included studies.

Author & year	Design	Summary	Participants *n* (Female%)	Setting	Age Mean (SD/range)	Intervention and duration	Intervention: psychological only (P) or mixed (M)/ group (G) or individual (Ind)	Anxiety outcome measure / when anxiety was assessed	Anxiety-related findings
Buszewicz 2006	RCT	Self-management programme + educational booklet vs. educational booklet only for OA patients	Patients with hip and/or knee OA T: *n*=406 (63%) C: *n*=406 (63%)	PC Comm	T: 68.4 (8.2) C: 68.7 (8.6)	*Challenging Arthritis*: self-management programme provided by Arthritis Care, based on social cognitive theory. 6 sessions.	M / G	HADS – anxiety subscale / Pre, post, 4 month fu & 12 month fu	Significant reduction in anxiety at 12 months follow-up, not at 4 months, for both T and C. T=C.
Giraudet-Le Quintrec 2003	RCT	Educational session (T) vs. TAU (C) for patients pre and post hip replacement surgery	Patients with hip OA scheduled for hip replacement surgery T: *n*=48 (50%) C: *n*=52 (62%)	Hospital OP	T: 62.7 (8.8) C: 64.3 (9.5)	Multidisciplinary educational session, including discussion of emotional preparation prior to surgery with a Psychiatrist. 1 session, approx. 2.5 hours	M / G	STAI / Pre, post, fu 1-7 days after surgery	T was significantly less anxious post-treatment compared to C. T<C. Difference not maintained at post-surgery follow-up.
Jessep 2009	RCT	Rehabilitation programme (T) vs. outpatient physiotherapy (C) for knee OA patients	Patients with knee OA T: *n*=29 (76%) C: *n*=35 (63%)	PC Comm & OP	T: 66 (53-81) C: 67 (51-76)	*ESCAPE-knee pain*: self-management programme for knee OA to change behaviour and challenge unhelpful beliefs. Includes exercise programme. 10 sessions, 60 minutes long each, 2x weekly for 5 weeks	M / G	HADS – anxiety subscale / Pre, post & 12 month fu	No significant difference in anxiety for T post-intervention. No between-group differences. T=C.

Key. SD: standard deviation; T: treatment group; C: control group; TAU: treatment as usual; PC: primary care; Comm: community; OP: outpatients; TSK: Tampa Scale of Kinesiophobia; STAI (Spielberger State-Trait Anxiety Inventory); HADS: Hospital Anxiety and Depression Scale; NRS: numerical rating scale; PASS: Pain Anxiety Symptom Scale; fu: follow-up.

Laborde 1983	RCT	Information brochure (T1) vs. joint preservation education + T1 (T2) vs. relaxation + T1 (T3) vs. T2 + relaxation (T4) vs. no treatment (C) for OA patients	Patients with OA T1: *n*=35 (not reported) T2: *n*=35 (not reported) T3: *n*=35 (not reported) T4: *n*=35 (not reported) C: *n*=20 (not reported)	Comm	All participants: 40-59: 14% 60-79: 69% 80-90+: 17%	Physiological educational leaflet about OA, joint preservation education and relaxation in a variety of combinations. Interventions including relaxation are only interventions with a psychological component. Duration of interventions unclear.	M (T3 and T4 only) / Ind	NRS assessing OA pain-related stress on a 1-10 scale / Pre & post	No intervention effects found for OA pain-related stress. All treatment groups=C.
Wetherell 2011 *** OA sample only**	RCT	CBT (T1) vs ACT (T2) for chronic pain patients, including an OA sample	Patients with OA T1: *n*=23 (57%)* T2: *n*=15 (53%)*	Comm	T1: 57.6 (11.1)* T2: 60.1 (10.7)*	CBT or ACT. 8 weekly sessions, 90 minutes long.	P / G	PASS – short form / Pre x2, post & 6 month fu	Reduced pain-related anxiety after both psychological interventions. No between-group differences. T1=T2.
Williams 2011	RCT	Educational booklet (T) vs. control booklet (C) for OA patients	Patients with hip and/or knee OA T: *n*=59 (64%) C: *n*=60 (63%)	PC Comm	T: 68.2 (8.1) C: 68.6 (8.5)	*The Hip & Knee Book*: educational self-help material to challenge unhelpful beliefs and encourage exercise, based on psychological theory of self-regulation of illness and treatment beliefs	M / Ind	TSK / Pre, 1 month fu & 3 month fu	Reduction in fear of movement beliefs for T at 1 and 3 month follow-up. T<C.

Key. SD: standard deviation; T: treatment group; C: control group; TAU: treatment as usual; PC: primary care; Comm: community; OP: outpatients; TSK: Tampa Scale of Kinesiophobia; STAI (Spielberger State-Trait Anxiety Inventory); HADS: Hospital Anxiety and Depression Scale; NRS: numerical rating scale; PASS: Pain Anxiety Symptom Scale; fu: follow-up.

Most of the studies were European: 3 from the UK (Buszewicz 2006; Jessep 2009; Williams 2011) and 1 from France (Giraudet-Le Quintrec 2003). Two of the studies included were from the USA (Laborde 1983; Wetherell 2011). Five studies were conducted in community settings (Buszewicz 2006; Jessep 2009; Laborde 1983; Wetherell 2011; Williams 2011) and the sixth study was undertaken in a hospital surgical outpatient and inpatient setting (Giraudet-Le Quintrec 2003). Three studies (Buszewicz 2006; Laborde 1983; Williams 2011) were multicentre trials: the other 3 trials were conducted within a single centre.

Only patients with OA were included in the study samples, except for in the Wetherell study (Wetherell 2011). Wetherell 2011 included participants with other chronic pain diagnoses: however, only the OA sample data was analysed for the purposes of this review (this data was accessed *via* personal communication with the study author).

Method of participant assignment:

All of the included studies were RCTs: no CCTs were included after the execution of the inclusion and exclusion criteria. None of the studies reported the method of generating the random sequence. In four of the studies, participants were independently assigned to intervention groups (Buszewicz 2006; Jessep 2009; Williams 2011; Wetherell 2011), and Giraudet-Le Quintrec 2003 used a sealed envelope randomisation method. The randomisation method was not reported in Laborde 1983.

Blinding:

Three studies were single-blind RCTs (Buszewicz 2006; Williams 2011; Wetherell 2011). Outcomes (including anxiety outcomes) were assessed by study personnel who were blind to the participants' treatment allocation in all of the studies, except for Giraudet-Le Quintrec 2003 and Laborde 1983. Giraudet-Le Quintrec 2003 was unblinded: however, the authors did include a comment of how they thought this would have had minimal effect on the data due to the use of patient self-report measures. Blinding was not reported in Laborde 1983.

Participants:

All studies included individuals with OA, with two studies including participants with OA at any body site (Laborde 1983; Wetherell 2011). Two studies included patients with hip and/or knee OA only (Buszewicz 2006; Williams 2011). Jessep 2009 included patients with knee OA only, and all participants in Giraudet-Le Quintrec 2003 had hip OA and were scheduled for hip replacement surgery.

The number of participants in the studies were varied, ranging from 38 (Wetherell 2011) to 812 (Buszewicz 2006). There was also wide variation in the number of participants in the treatment and control groups (smallest group size: 15 in Wetherell 2011, and largest group size: 406 in Buszewicz 2006). Participants in all studies were aged 40 or over, with most participants being in their 60s. The percentage of females included in treatment and control groups varied from 50% (Giraudet-Le Quintrec 2003) to 76% (Jessep 2009). One study did not report gender ratios (Laborde 1983).

Interventions:

Four of the trials studied group interventions (Buszewicz 2006; Giraudet-Le Quintrec 2003; Jessep 2009; Wetherell 2011), and 2 studies investigated individual treatments (Laborde 1983; Williams 2011). All studies except for Wetherell 2011 included multidisciplinary mixed interventions which included a psychological component. Wetherell 2011 investigated two 'pure' psychological interventions: Cognitive Behavioural Therapy (CBT) and Acceptance and Commitment Therapy (ACT).

Two of the group intervention studies included multidisciplinary self-management programmes (Buszewicz 2006; Jessep 2009). One group intervention study included a multidisciplinary pre-surgery education session in which there was a discussion of emotional preparation before surgery (Giraudet-Le Quintrec 2003). Laborde 1983 investigated 2 mixed interventions which included relaxation (the psychological component). All studies except for Williams 2011 included

interventions which were administered by healthcare professionals. The Williams study (Williams 2011) investigated the effectiveness of an educational self-help booklet, although these materials were developed by healthcare professionals.

The psychological components of four of the five mixed intervention studies (Buszewicz 2006; Jessep 2009; Laborde 1983; Williams 2011) were all based on cognitive-behavioural theory. The psychological theory underpinning the psychological component of the intervention in one study (Giraudet-Le Quintrec 2003) was not specified. However, the intervention was classed as containing a psychological component due to the involvement of a mental health professional in a question and answer session about mood.

All but 2 studies compared 1 treatment intervention to 1 control intervention. In Laborde 1983, 4 treatment interventions (2 of which included a psychological component) were compared to a control. In Wetherell 2011, there was no control intervention: 2 psychological interventions were compared.

Anxiety outcomes:

All studies used standardised, reliable and valid questionnaires to assess anxiety, except for Laborde 1983 which assessed anxiety using an NRS. Three studies assessed generalised anxiety, using the following questionnaires:

- Hospital Anxiety and Depression Scale (HADS; Zigmond 1983): Buszewicz 2006 and Jessep 2009;
- Spielberger State-Trait Anxiety Inventory (STAI; Spielberger 1983): Giraudet-Le Quintrec 2003.

Two studies assessed pain-related anxiety (Laborde 1983; Wetherell 2011). Laborde 1983 specified to participants that this measure only included anxiety caused by pain related to their OA. The Wetherell study (Wetherell 2011) assessed anxiety caused by any pain experienced. Pain-related anxiety was assessed in these 2 studies using the following measures:

- Pain Anxiety Symptom Scale (PASS; McCracken 1993): Wetherell 2011;
- A 1-10 numerical rating scale (NRS; Huber 2007): Laborde 1983.

One study (Williams 2011) assessed fear of movement (kinesiophobia) using the following questionnaire:

- Tampa Scale of Kinesiophobia (TSK; Vlaeyen 1995).

All studies assessed anxiety pre- and post-intervention. Three studies also measured anxiety at follow-up at least 6 months post-intervention (6 months follow-up: Wetherell 2011; 12 months follow-up: Buszewicz 2006 and Jessep 2009).

Risk of bias in included studies

The risk of bias in the included studies was generally low (see Table 2). The risk of each type of bias was unclear for at least 1 study, usually due to lack of information.

Table 2. Summary of risk of bias judgements for the included studies.

	Random sequence generation (selection bias)		Allocation concealment (selection bias)		Blinding (performance & detection biases)		Incomplete outcome data (attrition bias)		Selective reporting of outcomes (reporting bias)	
		Evidence		Evidence		Evidence		Evidence		Evidence
Buszewicz 2006	Unclear	No information	Low	Centralised and computer-based	Low	Study team blinded (except for trial manager)	Low	Intention-to-treat used	Unclear	Protocol not available and unclear from paper
Giraudet-Le Quintrec 2003	Unclear	No information	Low	Sequentially numbered, opaque, sealed envelopes	High	Unblinded and limited information regarding the impact	Unclear	Intention-to-treat not used, 1 drop-out	Unclear	Protocol not available and unclear from paper
Jessep 2009	Unclear	No information	Low	Centralised	Unclear	Assessor blinded, no further information	Low	Intention-to-treat used	Unclear	Protocol not available and unclear from paper
Laborde 1983	Unclear	No information	Unclear	No information	Unclear	No information	Low	No missing data	Unclear	Protocol not available and unclear from paper
Wetherell 2011	Unclear	Computer-generated for block randomisation but no information about generation of sequence for assignment to block groups	Low	Centralised and computer-based	Low	Study team blinded (except for one therapist who had no patient contact pre-intervention), participants blinded before intervention began	Low	Intention-to-treat used	Unclear	Protocol not available and unclear from paper
Williams 2011	Unclear	No information	Low	Centralised	Low	Assessors and data collectors blinded	Low	Intention-to-treat used	Low	Protocol available and all outcomes reported

Random sequence generation (selection bias)

The random sequence generation was not reported for all studies, except for Wetherell 2011, in which it was reported but lacked sufficient details in order to assess the risk of bias. Therefore, the risk of bias was rated as unclear for all studies.

Allocation concealment (selection bias)

Allocation to groups was effectively concealed in 5 studies *via* a centralised independent system (Buszewicz 2006; Jessep 2009; Williams 2011; Wetherell 2011) or by using sequentially numbered, opaque, sealed envelopes (Giraudet-Le Quintrec 2003), and so the risk of bias was assessed as low. The method by which participants were allocated to groups was not reported in Laborde 1983, and so the risk of bias was assessed as unclear.

Blinding (performance and detection biases)

Three studies (Buszewicz 2006; Williams 2011; Wetherell 2011) were single-blinded and so were assessed as having a low risk of bias in performance and detection. One study (Giraudet-Le Quintrec 2003) was unblinded, although the study authors did comment that they felt the lack of blinding would not have had a substantial effect on the results due to the use of patient self-report outcome measures. The reviewer (VT) did not feel this justification was sufficient or convincing, and so the risk of bias was assessed as high. Blinding was not reported in Laborde 1983, and so the risk of bias was assessed as unclear.

Incomplete outcome data (attrition bias)

Attrition bias was assessed as low for five of the included studies for the following reasons: no data were missing (Laborde 1983); or the intention-to-treat principle was used (Buszewicz 2006; Jessep 2009; Wetherell 2011; Williams 2011). One study (Giraudet-Le Quintrec 2003) did not use intention-to-treat analysis and there was 1 drop-out. Therefore the risk of attrition bias in this study was rated as unclear.

Selective reporting of outcomes (reporting bias)

Reporting bias was rated as unclear for all studies except for Williams 2011, as the protocols were unavailable for these trials and the reporting bias was not able to be assessed from the available information. The Williams study (Williams 2011) was assessed as having a low risk of bias due to the protocol being available and no selective reporting was evident.

Other biases

No other biases were evident in any of the studies, so other biases were assessed as low (not included in Table 2).

Effects of interventions

Two studies reported significant differences in anxiety between treatment and control groups post-intervention, with a reduction in anxiety evident in the treatment groups after intervention (Giraudet-Le Quintrec 2003; Williams 2011). Giraudet-Le Quintrec 2003 concluded that the reduction in generalised anxiety was not maintained after hip replacement surgery. In contrast, however, the Williams study (Williams 2011) reported that the differences in fear of movement beliefs (assessed using TSK) were significant at both 1 and 3 month follow-up.

One study (Buszewicz 2006), concluded that there was a significant reduction in generalised anxiety following intervention, although this was also reported for the control group. This difference in pre- and post-intervention anxiety for both the treatment and control groups was reported as significant at the 12 month, but not 4 month, follow-up.

In the only equivalence RCT included in this review, as well as the only included study which investigated ‘pure’ psychological treatments (Wetherell 2011), it was concluded that there were significant differences between pre- and post-intervention pain-related anxiety for both treatment groups (CBT and ACT). The study reported that these differences were maintained for both treatment groups at 6 month follow-up.

Two studies (Laborde 1983; Jessep 2009) reported no differences in anxiety levels between treatment and control groups post-intervention. The Laborde study (1983) assessed pain-related anxiety, and concluded that there were no differences between any of the 4 treatment groups (2 of which included a psychological component) or the control group. However, it is important to be cautious of this finding as anxiety was assessed using a non-standardised outcome measure. The Jessep study (Jessep 2009) concluded that there were no differences in generalised anxiety between the treatment and control groups post-intervention. Jessep 2009 reported that this lack of significant difference was maintained at 12 month follow.

Effects of interventions on different types of anxiety

Generalised anxiety

The conclusions of the 3 studies which assessed the effects of interventions on generalised anxiety (Buszewicz 2006; Giraudet-Le Quintrec 2003; Jessep 2009) were varied. Only one of these studies (Giraudet-Le Quintrec 2003) reported a significant reduction in generalised anxiety post-intervention compared to the control group, and this difference was reported to not be maintained at follow-up. However, as Giraudet-Le Quintrec 2003 studied patients about to have joint replacement surgery, this sample may differ considerably from the samples in the other included studies, and so any narrative comparison should be considered with caution.

Pain-related anxiety

The conclusions of the 2 studies which investigated the effects of interventions on pain-related anxiety (Laborde 1983; Wetherell 2011) varied considerably. One study (Wetherell 2011) reported a significant difference between pre- and post-intervention pain-related anxiety. However, the OA subgroup of this study had very small sample sizes (CBT group, *n*=15; ACT group, *n*=23) and no control was included; therefore, this conclusion should be taken with caution. Furthermore, the validity of this narrative comparison between Laborde 1983 and Wetherell 2011 should be taken with caution as Laborde 1983 assessed anxiety specifically

related to OA pain, whereas Wetherell 2011 measured anxiety related to any type of pain.

Fear of movement

Kinesiophobia was only investigated by one study (Williams 2011) and so no between-studies narrative comparisons can be made.

Effects of psychological interventions vs. mixed interventions on anxiety

As only one study investigated the effectiveness of a 'pure' psychological intervention (Wetherell 2011), it was not possible to compare the effects on anxiety of such interventions to that of mixed interventions which include a psychological component.

DISCUSSION

Summary of main results

The effectiveness of psychological interventions, particularly self-management programmes which include a psychological component, for individuals with OA has been investigated for some time, particularly over the last 15 years. Despite the strong association between OA and anxiety, the effectiveness of psychological interventions on reducing anxiety in OA has not been extensively investigated.

This review included 6 RCTs which assessed the effect of psychological interventions on anxiety in people with OA. The majority of the interventions were based on cognitive-behavioural theory, which is likely to be associated with the prevalence of this model in OA and chronic pain literature. All but one of these studies were published in the last decade. The quality of the studies was quite low, with many not meeting all of the CONSORT guidelines (Moher 2001), particularly in relation to the reporting of the randomisation process and blinding.

All but one study used standardised outcome measures of anxiety. The sample sizes were fairly small in all studies, except for in Buszewicz 2006.

The results of this review suggest that there is some evidence to support the use of psychological treatments to reduce anxiety in people with OA. However, due to the low number and the poor methodological quality of included studies, further high quality research trials are needed. Much more research investigating the effect of 'pure' psychological interventions on anxiety variables in OA is needed. With regards to mixed interventions, there is currently little research addressing the effects of the different components of the interventions, including the psychological components, on anxiety or other factors (Gay 2002).

Quality of the evidence

The evidence base investigating the effect of psychological interventions on anxiety in OA is relatively poor. Only six studies were identified, and all but one trial (Buszewicz 2006) involved small samples. The CONSORT guidelines (Moher, 2001) for the reporting of RCTs were not followed strictly by any of the included studies. In particular, the blinding procedure was only adequately reported in 3 of the studies (Buszewicz 2006; Wetherell 2011; Williams 2011).

The selection of outcome measures to assess anxiety was suitable in all studies, due to the use of commonly use measures in OA and chronic pain literature and clinical practice. However, one study (Laborde 1983) used a numerical rating scale (NRS) measure, which could be criticised for being non-standardised, which could affect the quality of the anxiety data collected in this study. It is important to note, though, that the use of NRS anxiety measures in chronic pain research has been advocated and supported by a number of publications (Huber 2007).

Potential biases in the review process

One reviewer (VT) conceptualised and undertook all aspects of the review, and so the inclusion and bias decisions were not verified by the other review authors.

In future versions of this review, it will be important that multiple reviewers are involved in the process in order to limit decision bias.

AUTHOR'S CONCLUSIONS

Implications for practice

Anxiety difficulties are often experienced by people with OA. Psychological interventions or multidisciplinary interventions which include a psychological component can be offered to OA patients, and are becoming a much more routine treatment option in OA. The effect of such interventions on anxiety has not been as routinely investigated compared to factors such as depression and pain. This review found some evidence for the use of psychological interventions, delivered alone or as part of a multidisciplinary treatment, in reducing anxiety in people with OA. However, this should be treated with caution as there were a low number of studies with small sample sizes, and the studies were of fairly poor quality.

Implication for research

There is little research to draw conclusions about the effectiveness of psychological interventions in reducing anxiety in OA patients. Further high-quality research is required, particularly investigating 'pure' psychological interventions as these are much less commonly researched compared to mixed interventions which include a psychological component. Regarding multidisciplinary interventions, it is also important that future research investigates which aspects of the treatment affect anxiety outcomes.

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Journal paper

This journal paper is formatted for submission to *Osteoarthritis and Cartilage.*

Associations Between Pain Pressure Thresholds and Self-Reported Pain, Depression, Anxiety, and Gender in Knee Osteoarthritis

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Running title: Pain thresholds and mood in knee OA

Abstract

Objective

To investigate the association between pain pressure thresholds (PPTs) and self-reported pain, depression, anxiety, and gender in knee osteoarthritis (OA).

Method

Quantitative sensory testing (QST) measuring PPTs was undertaken on 77 participants with knee OA, recruited through healthcare services in the United Kingdom. PPTs were measured at the sternum, medial and lateral knee joint-lines, and medial tibia mid-shaft. Participants completed subjective measures of pain, depression and anxiety.

Results

Small-to-medium, statistically-significant correlations (with *P*-values ranging from .006 to .049) were found between PPTs and gender (r_{rb} = -.29 to -.36; female gender was associated with lower PPTs) and between PPTs and at least one mood variable (r_s = -.23 to -.37). Self-reported knee pain was significantly correlated with the lateral joint-line PPT (r_s = -.28, *P* = .015), but not with the other PPTs. The parallel hierarchical multiple regression models for each body site PPT were statistically significant, and the predictor variables (gender, pain, depression and anxiety) explained between 13 and 18% of variation in PPTs. Gender was the only factor that significantly contributed to these models: female participants generally reported lower PPTs than male participants.

Conclusions

This study suggests that gender, self-reported pain, depression and anxiety contribute to PPT variation in knee OA. As QST might measure central sensitisation, the findings could suggest that these factors are involved in central pain processing in knee OA. However, the gender differences could have been due to demand characteristics elicited by the QST procedure, which appears an important area for future research.

Abstract word count: 250 words (maximum: 250 words)

Keywords: knee osteoarthritis; pain threshold; depression; anxiety.

Introduction

It is widely recognised that joint pain is the main symptom of knee osteoarthritis (OA), the most common form of OA [1]. Pain due to knee OA has been found to be associated with reduced physical and psychological health [2]. Therefore, it is important for clinicians and researchers to accurately assess pain in knee OA in order to provide appropriate interventions to improve quality of life.

Assessment of pain

Pain in knee OA is often assessed using subjective unidimensional self-report measures, such as a numeric rating scale (NRS) or visual analogue scale (VAS), which require the patient to rate the intensity of their pain on a linear scale [3]. Multidimensional self-report questionnaires have also been developed to measure pain in knee OA, such as the Intermittent and Constant Osteoarthritis Pain questionnaire [4]. One criticism of subjective self-report measures of pain is that they are not able to identify underlying pain mechanisms [5]. This is important in knee OA, as it has been argued that the experience of pain may be affected by peripheral nociceptive mechanisms and by *central sensitisation* [6].

Central sensitisation

Central sensitisation is defined as “increased responsiveness of nociceptive neurons in the central nervous system” [7]. Central sensitisation is thought to result in increased sensitivity to pain [6, 8], both at the site of tissue damage (*ie*, the knee in knee OA) and at body sites remote from the affected area [6], although increased sensitivity at remote areas is thought to be particularly indicative of central sensitisation [9]. Central sensitisation has been implicated in the experience of pain in knee OA [9, 10], which therefore challenges the dominant understanding of pain in the condition as having a purely nociceptive mechanism [8]. Central sensitisation may be linked to repeated nociception and psychological factors [6]. However, this has not been investigated extensively, particularly the link between central sensitisation and psychological factors (in terms of cognition, emotion, and/or behaviour) [6, 11].

Although central sensitisation is discussed in much of the literature as an objective and real mechanism of pain in knee OA and other painful conditions [8], it could be criticised for being a circular concept, in that it proposes that more experience of pain leads to more pain.

Quantitative sensory testing

Despite the potential issues with central sensitisation as a concept, much interest has been paid to how such a mechanism could be measured [8]. Quantitative sensory testing (QST) is considered one such method [6]. QST has been described as a 'semi-objective' measure of pain [12], which involves the controlled application of a stimulus to body areas [13]. Different stimuli have been used in QST, including pressure, temperature, chemical, and electrical stimuli [14]. Pressure algometry which measures pain pressure thresholds (PPTs) has been found to be the most reliable form of QST in knee OA [15], and has been used in previous knee OA studies [eg, 9, 10, 16].

PPTs in knee OA have been found to be negatively correlated with self-reported pain (*ie*, the lower the PPT, the higher the self-reported pain) [10]. PPTs have also been found to be negatively correlated with psychological factors such as depression and anxiety in knee OA patients [9] (*ie*, the lower the PPT, the higher the level of depression and anxiety). If one accepts the suggestion by many researchers that QST data (such as PPTs) provide a quantification of central sensitisation [6], these findings could suggest that mood plays a role in the relationship between pain and central sensitisation in knee OA. However, the relationships between mood, pain and PPTs have not been the main focus of previous research, and so this has not been investigated in detail.

Depression and anxiety

Pain has been described as a multifactorial experience which includes the role of psychological factors (with depression and anxiety being the most researched psychological variables in chronic pain samples) [17]. Prevalence rates of depression and anxiety for knee OA patients living in the community have been reported at over 20% [18], which is higher than the approximate 17% prevalence

rate of depression and anxiety in the general older adult population [19, 20]. Riddle and colleagues [18] found significantly higher pain intensity ratings in knee OA patients with clinical levels of depression and anxiety, compared to those without. Furthermore, in past knee OA research, higher levels of anxiety and depression have frequently been associated with higher self-reported knee pain intensity [eg, 21, 22]. Depression and anxiety are also perceived as a key problem in OA by patients [23]. Therefore, depression and anxiety appear to be important factors in the experience of pain in knee OA, and may be associated with higher levels of self-reported pain intensity.

The link between knee OA pain, anxiety and depression could be explained by a number of psychological models, such as the fear-avoidance model of chronic pain [24], which is arguably the most prolific psychological explanatory model of the links between pain and mood in musculoskeletal disorders [25]. This cognitive-behavioural model suggests that pain (*eg*, due to knee OA) leads to anxiety if the individual appraises the pain in a catastrophising manner [24]. The fear-avoidance model proposes that individuals experiencing pain-related anxiety use avoidance strategies (such as reducing activity levels) as an attempt to reduce the anxiety experienced [24]. According to this model, avoidance of physical activity can lead to disability and depression, which maintains, and can even increase, the pain experienced [24]. Disability and depression can maintain/increase pain due to disuse of the body part (*eg,* knee) which can lead to further physical pathology and increased pain [25]. The experience of pain can also be increased via cognitive-behavioural processes linked with distress [25], such as the individual focussing more on their pain and physical health problems, which could cause them to perceive more pain.

Pincus and colleagues [26] extended the fear-avoidance model to account for the experiences of patients who feel depressed prior to the onset of a painful condition. They propose that, for these patients, pre-existing depression may increase the likelihood of an anxiety response to the experience of chronic pain.

Gender

Gender has also been highlighted as a key factor in knee OA: a meta-analysis found women to have a higher risk of both prevalence and incidence of knee OA compared to men [27]. Also, women have repeatedly been found to report higher levels of pain than men in chronic pain and healthy samples [28]. Potential explanations of this gender difference include: biological factors (*eg,* hormonal processes [28]); psychological factors (*eg*, higher prevalence of depression and anxiety and increased monitoring of bodily sensations in females compared to males [29]); and sociological factors (differences in gender socialisation, and expectations and responses from others regarding pain [30]).

Gender differences have also been found in QST-assessed pain, with women showing lower PPTs in healthy samples [31, 32]. However, the role of gender has not been the focus of the majority of QST studies investigating knee OA and, when it has, a gender difference has not been consistently found [33]. In terms of the impact of psychosocial factors on gender differences in QST-assessed pain, a systematic review by Racine and colleagues [34] concluded that there was limited evidence for the role of depression on gender differences in QST-assessed pain, and inconclusive and contradictory evidence for the role of anxiety.

Aims

QST (such as that measuring PPTs) has been suggested as a potential tool for identifying patients who may require non-medical interventions (*eg,* psychological therapy) [35]. It is therefore important to develop a more comprehensive understanding of PPTs and of how they relate to other factors. Specifically, the aim of the current study was to investigate the association between PPTs and the key related factors in the literature: self-reported pain, gender, anxiety, and depression for people with knee OA, as this has not previously been examined in detail.

Method

Participants

Seventy-seven participants were recruited from: 1. National Health Service (NHS) orthopaedic/musculoskeletal clinics within Nottingham University Hospitals NHS Trust and Sherwood Forest Hospitals NHS Trust; and 2. NHS General Practice (GP) surgeries within Bassetlaw Primary Care Trust (PCT), Derby City PCT, Derbyshire County PCT, Nottingham City PCT, and Nottinghamshire County PCT and County Health Partnerships. All participants had a clinical diagnosis of knee OA and reported accompanying knee pain. We conducted a clinical examination of the knee to confirm diagnosis. Exclusion criteria were: aged under 18 years; joint surgery less than 3 months prior to study participation; inability to speak and understand English; and a comorbid diagnosis of an inflammatory arthritic disorder (*eg*, rheumatoid arthritis). Inclusion criteria (*ie*, knee OA with pain) and exclusion criteria were assessed in two ways: 1. Recruiting gatekeeping professionals were asked to only invite people who met the inclusion criteria and avoid inviting those who met the exclusion criteria; and 2. Participants were asked to screen themselves as part of the study invitation.

Informed consent was obtained from all participants, and the study received ethical approval from Nottingham Research Ethics Committee one and governance permissions from each of the NHS trusts involved.

Demographics

Demographic details (gender and age) were collected from participants to provide information regarding sample characteristics.

Quantitative sensory testing

The method of QST used was pain-pressure algometry measuring PPTs. An electronic pressure algometer, a laptop recording/display device, and a patient switch were used (Somedic, Sweden). The pressure algometer probe was 1cm in diameter and covered with a padded disc. The probe was applied to participants' skin with a steadily increasing pressure at a rate of 50 kilopascals per second (kPa/s) [36]. Participants were instructed to indicate when the

pressure stimulus had started to feel painful ('the first sensation of pain') by pressing a switch, at which time the researcher immediately removed the probe. The amount of pressure being applied immediately before the probe was removed was recorded for each test. This is the 'method of limits' form of QST, which is the most commonly used approach due to being less time-consuming than other forms of QST [13]. All QST was undertaken in a clinic room at a University of Nottingham and Arthritis Research UK Pain Centre research department by one of two trained researchers. The inter-rater reliability of conducting QST was investigated as part of a separate study and was found to be acceptable.

PPTs were measured for five different body sites by the researcher, in the following order: 1. Fingernail bed (as a learning site for the participant to ensure they fully understood the procedure and instructions); 2. Sternum; 3. Medial knee joint-line; 4. Lateral knee joint-line; and 5. Medial tibia mid-shaft. The knee and tibia sites tested were those on the same leg as the knee OA for that individual. In cases where bilateral knee OA was present, QST was undertaken on the leg with the most painful knee (as decided by the participant prior to testing). Body sites were chosen based on a systematic review of previous QST studies with OA participants [14]. Each body site was tested 3 times, with an interval of two minutes between each test to protect against 'wind-up' effects. A mean of the three PPTs for each body site was calculated and used in the analysis, as in previous QST research [16, 37, 38].

Questionnaires

Before the QST, participants had completed questionnaires, *via* the postal system, evaluating pain and psychological factors. This research is part of a wider study (yet to be published) which aims to investigate the utility of questionnaires measuring a variety of psychological factors in knee OA patients. As depression and anxiety are factors of interest in this study, data from the Beck Depression Inventory II (BDI-II; [39]) and the Spielberger State-Trait Anxiety Inventory short form (STAI-SF; [40]) were included in the analysis. Reliability and validity of these measures have been demonstrated previously (BDI-II: [41]; STAI-SF: [40]). Furthermore, another study by the research team (as yet unpublished) explored

the psychometric properties of the STAI-SF in a knee OA sample using Rasch analysis and found acceptable model fit.

Pain NRS

On the day of the QST, participants were asked to rate the intensity of the average pain they had experienced in the previous week in their most painful knee from 0-10 (where 0 represented no pain and 10 represented extreme pain). NRS measures of pain have been used in previous QST research in knee OA [16].

Statistical Analysis

Spearman's correlation (r_s) analyses were used to determine the association between pain (NRS), depression (BDI-II), anxiety (STAI-SF), and mean PPTs for each body site. Rank-biserial (r_{rb}) correlations were conducted to analyse the relationships between gender and the other study factors. Hierarchical (two-stage) multiple linear regression analyses were undertaken for each of the four PPTs (excluding the fingernail learning site), with gender entered in the first block, and pain NRS, depression (BDI-II) and anxiety (STAI-SF) in the second block. All predictor factors (gender, pain NRS, depression, and anxiety) were entered into the regression models, regardless of statistical significance, as there was judged to be a theoretical rationale for this based on the existing literature. Missing data were assessed and where appropriate values were imputed using a maximum likelihood procedure. Assumptions of multiple regression were analysed and square-root transformations were applied to the mean PPT for each body site and to the depression (BDI-II) data accordingly. One data point in the medial tibia mid-shaft PPT was also adjusted to reduce the impact of a univariate outlier. Residuals were investigated to ensure that no further assumptions were violated. SPSS version 21 was used for the analysis and, for the correlational and multiple regression statistics, significance was set at $P < .05$.

Results

Participant demographics, PPTs for each body site, and anxiety, depression and pain NRS scores and are presented in Table 3.

Table 3

Participant demographics, PPTs, and pain NRS, depression and anxiety scores

	Mean (SD)
Age (years)	67.68 (9.44)
Gender distribution (*n*; %)	Female (*n* = 43; 55.8%)
	Male (*n* = 34; 44.2%)
Mean PPTs (kPa):	
Sternum	229.72 (143.58)
Medial joint line	292.96 (178.75)
Lateral joint line	311.85 (178.99)
Medial tibia mid-shaft	194.02 (118.78)
	Median (IQR)
Pain NRS *(possible score: 1 – 10)*	7.00 (5.00 – 8.00)
Depression (BDI-II) *(possible score: 0 – 63)*	10.00 (4.50 – 15.00)
Anxiety (STAI-SF) *(possible score: 6 – 24)*	10.00 (7.00 – 13.75)

Correlations

See Table 4 for a summary of the correlations between the PPT means and gender, pain NRS, depression, and anxiety, which were all of small or medium size [42].

Table 4

Correlation coefficients between PPT means and the study variables of interest

	PPT mean			
	Sternum	*Medial joint-line*	*Lateral joint-line*	*Medial tibia mid-shaft*
Gender [a, c]	-.29 *	-.36 **	-.31 *	-.31 *
Pain NRS [b]	-.21	-.15	-.28 *	-.13
Depression [b]	-.30 **	-.22	-.28 *	-.37 **
Anxiety [b]	-.25 *	-.25 *	-.23 *	-.31 **

Note. [a] Rank-biserial correlation coefficients were calculated when gender was an included factor; [b] Spearman's correlation coefficients were calculated when gender was not an included factor; [c] Gender was dummy coded as 0 = male and 1 = female; * $P <$ .05; ** $P < .01$.

The relationships between the PPT means and pain NRS, depression and anxiety were negatively correlated, meaning that lower PPTs (*ie*, higher pain sensitivity) were associated with higher pain NRS, depression, and anxiety scores. The significant correlation between gender and each PPT mean was due to higher mean PPTs (for all body sites) for males compared to females (see Table 5).

Table 5

Mean PPTs for each body site for males and females

Gender	**PPT (kPa): mean (SD)**			
	Sternum	*Medial joint-line*	*Lateral joint-line*	*Medial tibia mid-shaft*
Female	189.32 (100.57)	238.66 (141.00)	262.05 (141.03)	160.74 (88.91)
Male	280.80 (172.59)	361.64 (198.95)	374.83 (202.85)	236.10 (138.42)

Although the correlations between the predictor variables were not the focus of this study, they are presented in Table 6 for information.

Table 6

Correlation coefficients between gender, pain NRS, depression and anxiety

Factor	*Pain NRS*	*Depression*	*Anxiety*
Gender [a, c]	.00	.18	-.06
Pain NRS [b]	-	.27 *	.27 *
Depression [b]	-	-	.62 **

Note. [a] Rank-biserial correlation coefficients were calculated when gender was an included factor; [b] Spearman's correlation coefficients were calculated when gender was not an included factor; [c] Gender was dummy coded as 0 = male and 1 = female; * $P < .05$; ** $P < .01$.

Multiple linear regression

The predictor factors were then entered into the multiple linear regression model for each PPT. Gender was dummy coded (0 = male; 1 = female), and was entered (as a dummy variable) into the multiple regression models first. Pain NRS, depression, and anxiety were entered together in the second stage. Four parallel multiple regression models were calculated (*ie*, one for each PPT site). Due to this multiple testing, the alpha values were corrected using Bonferroni-Holm adjustment. All regression models remained statistically-significant after this adjustment.

For the sternum PPT multiple regression (Table 7), the stage with gender alone explained 7% of the variation in sternum PPT (adjusted $R^2 = .07$), and the addition of depression, anxiety and pain NRS to the model explained 13% of the variation (adjusted $R^2 = .13$).

Table 7

Multiple hierarchical regression results for sternum PPT

Stage of hierarchical regression	Factors	*B*	*SE B*	β	Adjusted R^2 of model (% of PPT variance explained)	Adjusted R^2 change (% change)	*P* of model
Stage 1	Constant	15.99	0.76	-			
	Gender	-2.69	1.02	-.29 *	.07 (7%)	-	.010
Stage 2	Constant	20.67	1.92	-			
	Gender	-2.61	1.03	-.28 *			
	Depression	-0.22	0.54	-.06			
	Anxiety	-0.20	0.15	-.20			
	Pain NRS	-0.28	0.25	-.13	.13 (13%)	+ .06 (+ 6%)	.006

Note. * $P < .05$

For the medial joint-line PPT multiple regression model (Table 8), the addition of depression, anxiety, and pain NRS on top of gender in stage 2 increased the amount of explained variation in medial joint-line PPT from 10% to 15%.

Table 8

Multiple hierarchical regression results for medial knee joint-line PPT

Stage of hierarchical regression	Factors	*B*	*SE B*	β	Adjusted R^2 of model (% of PPT variance explained)	Adjusted R^2 change (% change)	*P* of model
Stage 1	Constant	18.29	0.84	-			
	Gender	-3.35	1.13	-.33 *	.10 (10%)	-	.004
Stage 2	Constant	22.79	2.12	-			
	Gender	-3.43	1.14	-.34 *			
	Depression	0.09	0.60	.02			
	Anxiety	-0.31	0.16	-.28			
	Pain NRS	-0.20	0.27	-.08	.15 (15%)	+ .05 (+ 5%)	.004

Note. * $P < .01$

For the lateral joint-line PPT multiple regression (Table 9), stage 1 (with just gender entered) explained 7% in PPT variance. The addition of depression, anxiety, and pain NRS to the model explained 15% of the variation in lateral joint-line PPT.

Table 9

Multiple hierarchical regression results for lateral knee joint-line PPT

Stage of hierarchical regression	Factors	*B*	*SE B*	β	Adjusted R^2 of model (% of PPT variance explained)	Adjusted R^2 change (% change)	*P* of model
Stage 1	Constant	18.59	0.84	-			
	Gender	-2.83	1.13	-.28 *	.07 (7%)	-	.014
Stage 2	Constant	24.67	2.09	-			
	Gender	-2.79	1.12	-.28 *			
	Depression	-0.18	0.59	-.04			
	Anxiety	-0.21	0.16	-.19			
	Pain NRS	-0.49	0.27	-.20	.15 (15%)	+ .08 (+ 8%)	.003

Note. * $P < .05$

For the medial tibia mid-shaft PPT multiple regression (Table 10), stage 2 (with all factors entered) increased the explained PPT variation from 8% (in stage 1) to 18%.

Table 10

Multiple hierarchical regression results for medial tibia mid-shaft PPT

Stage of hierarchical regression	Factors	*B*	*SE B*	β	Adjusted R^2 of model (% of PPT variance explained)	Adjusted R^2 change (% change)	*P* of model
Stage 1	Constant	14.72	0.68	-			
	Gender	-2.47	0.92	-.30 **	.08 (8%)	-	.009
Stage 2	Constant	18.88	1.68	-			
	Gender	-2.14	0.90	-.26 *			
	Depression	-0.65	0.48	-.20			
	Anxiety	-0.18	0.13	-.20			
	Pain NRS	-0.06	0.22	-.03	.18 (18%)	+.10 (+10%)	.001

Note. * $P < .05$; ** $P < .01$

Discussion

The finding of mostly small negative correlations between PPTs and depression and anxiety supports previous findings in knee OA [9], and suggests that mood does have a role in PPTs. This supports the application of the biopsychosocial

model of pain in knee OA [45], and could be explained by psychological models such as the fear-avoidance model [24].

The fear-avoidance model proposes that higher levels of depression and anxiety as a response to pain are caused by unhelpful cognitions (*eg*, catastrophic appraisals) and behaviours (*eg,* avoidance of physical activities). This could mean that a more anxious and depressed individual pays more attention to bodily processes and is more likely to appraise them in a negative manner [25]. Therefore, individuals with higher levels of depression and anxiety would be more likely to perceive bodily sensations as painful, which would likely result in lower PPTs if assessed using pressure QST.

If PPTs are accepted as a measure of central sensitisation (which, as discussed earlier in this article, is a contentious concept), then the results of this study *could* suggest a role of depression and anxiety in central sensitisation in knee OA. Using the fear-avoidance model, which proposes that depression and anxiety as a reaction to pain can lead to the experience of further pain [24] (*ie,* increased nociception), and as prolonged and repeated nociception is thought to be a likely cause of central sensitisation [6], it makes theoretical sense that higher levels of anxiety and depression could be involved in the transition from pain with a mechanical cause to pain also involving central sensitisation. However, a psychological explanation of the link between mood and PPTs does not require the inclusion of the 'central sensitisation' concept.

The correlations between knee pain intensity and the PPTs were of a similar size to those in past research [10]. However, Arendt-Nielsen and colleagues investigated this relationship by combining the PPTs for all body sites tested, rather than *via* separate correlational analyses for each body site as in the present study. Given the differences between the PPTs for each body site in the present research, it seems important that these correlations were analysed separately. The Arendt-Nielsen study also differs from the current study in that they measured peak pain intensity in the previous 24 hours, whereas we measured average pain intensity across the previous week.

The lack of significant correlations between pain NRS and the medial knee joint-line PPT supports Finan et al.'s finding [9] of no difference in QST measurements (including PPTs) at knee sites affected by OA between patients with high or low reported pain. However, the Finan et al. study did find differences in QST at sites remote to the affected knee between patients in the high or low reported pain groups, which the current study did not replicate.

Interestingly, the lateral knee joint-line was the only body site where higher pain intensity was significantly associated with lower PPTs, contrary to Finan et al.'s findings [9]. Arendt-Nielsen and colleagues [10] found that more knee OA patients with damage to the lateral tibiofemoral knee compartment had high knee pain ratings compared to those without damage to this site. Although we did not assess radiographic knee damage severity, it could be that high pain NRS was also associated with damage to the lateral knee compartment in our sample, and that this relationship resulted in the correlation between pain rating and lateral knee joint-line PPT. However, a previous study found no differences in knee PPTs between knee OA patients with high or low radiographic damage [9], although it is important to note that this study did not investigate damage in specific parts of the knee. The importance of this finding in the present study is unclear and the role of radiographic damage to different parts of the knee on QST measurements and self-reported pain could be an interesting question for future research.

Higher PPTs at remote body sites to the area of damage (*ie*, the knee) are considered more likely to suggest the presence of central sensitisation than higher PPTs at the knee itself (as the PPTs are likely to also be measuring aspects of the nociceptive pain) [9]. Therefore, the study's finding of slightly stronger correlations between the psychological factors (depression and anxiety) and the PPTs at the remote body sites (sternum and medial tibia mid-shaft) than those at the knee joint sites could suggest the involvement of depression and anxiety in the process of central sensitisation. However, these differences in correlation sizes are minimal, and so no clear conclusions can be drawn from this finding alone. Furthermore, it is unclear whether PPTs do actual quantify central sensitisation (or whether they are more representative of demand characteristics

present within the QST assessment) and whether central sensitisation is a helpful concept more generally.

The multiple regression models found that gender, depression, anxiety, and pain rating together explained between 13 and 18% of variance in PPT (dependent on PPT site). This suggests that these factors are important to consider in relation to PPTs, and the finding that they do not explain more variation is understandable given the multifactorial nature of pain [7].

The finding of gender differences in PPTs supports previous findings of lower PPTs in females compared to males in healthy samples [31, 32], although does not replicate a past finding of no gender difference in PPTs in people with knee OA [33]. Several conclusions could be drawn from these findings. Firstly, it could represent a true gender difference in central sensitisation pain processing for knee OA patients (which may be due to a combination of biological and psychosocial factors [44]). Secondly, it could have been affected by demand characteristics, in terms of the impact of gender role expectations of pain [45] (*eg*, males not wanting to 'admit' that their PPT had been reached during the QST). Finally, there could have been an effect of the gender of the researcher administering the QST: both testers were female, and past research has found higher QST pain values when participants were tested by a researcher of the opposite sex [46]. This study did not investigate the role of the QST administrators' gender on PPTs, but previous research [46] suggests that the presence of female testers may have influenced the male participants to report higher PPTs. Therefore, higher PPTs in the male participants could have less to do with a gender difference in pain sensitivity and more to do with gender role expectations and beliefs around how to present yourself as 'masculine' to women, regarding pain.

It is important to acknowledge several limitations of the study. Firstly depression and anxiety were not measured on the same day as pain rating and PPTs. Therefore, the data may not accurately reflect the state mood of the participants at the time of the QST, which could have impacted on the findings. Furthermore, the small role of depression and anxiety may be due to the measures used (BDI-

II and STAI-SF), which, although used in past knee OA research [eg, 21, 47], were not developed specifically for a knee OA or chronic pain population. Therefore, the use of a mood measure developed for this patient group (such as the Depression, Anxiety, and Positive Outlook Scale [48]) may have been more sensitive to mood differences in the sample. Finally, it may be that other psychological factors are more relevant to PPTs in knee OA than depression and anxiety, such as pain catastrophising (although Finan et al. found similarly small correlations between QST measures and this psychological factor [9]).

The main finding of the research is that gender, pain rating, depression, and anxiety have a role in PPTs at both knee and remote body sites in people with knee OA. Further research regarding the impact of tester characteristics (*eg,* age, gender, perceived authority) on QST data in knee OA would add a further level of understanding to these findings and to research in this area more broadly.

Contributions

All authors were involved in the conception of the study. Bryan Moreton led the recruitment for the study and the collection of the questionnaire data, and Victoria Tew was involved in the QST data collection. Victoria Tew analysed the data and drafted the journal article. Roshan das Nair and Bryan Moreton provided critical appraisal of the article, and Victoria Tew finalised and approved the final version of the article. Victoria Tew takes responsibility for the integrity of this work, and can be contacted at victoria.tew@hotmail.co.uk.

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Competing interest statement

The authors have no conflict of interest.

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Extended paper

A. Extended Background

This extended background section will include an explanation of knee osteoarthritis (OA) and of theories of chronic pain. Psychological factors of interest in this research (namely anxiety and depression) will be explored, and further details of psychological models developed to explain the links between anxiety, depression and pain will be provided. The use of QST to assess pain sensitivity will be discussed, and a rationale for the research and its three component sub-studies will be provided. I will then go on to provide background information specific to the three sub-studies included in this research.

Osteoarthritis (OA) is the most common form of arthritis in the UK, affecting an estimated 8.5 million people (Arthritis Care, 2004). OA is characterised by tissue damage and abnormal bone growth at the affected body site (Arden & Nevitt, 2006), and is most commonly diagnosed in people aged over 45 years (Peat, McCarney, & Croft, 2001). The knee joint is the body site most commonly affected by OA (Arden & Nevitt, 2006). In a UK primary care setting, Peat et al. (2001) found that 18.1% of patients aged over 55 years had a diagnosis of knee OA. Given the increasingly ageing population in the UK, prevalence of knee OA, as an age-related disorder, is set to increase. This will therefore lead to increased service-provision and financial pressures on the NHS, with the National Institute for Clinical Excellence seeking to reduce costs of knee OA assessment and treatment (National Institute for Health and Clinical Excellence, 2008). Joint pain is the main symptom of knee OA (Arden & Nevitt, 2006), and therefore it is highly important that accurate assessment of pain is undertaken in this patient group. It has been suggested that pain, rather than mechanical knee damage, is actually the key 'problem' for many knee OA patients, although pain in knee OA has received much less research interest historically (Jordan & Gracely, 2013). In this thesis, the term 'pain' refers to chronic pain (that is, persistent pain associated with an injury or disease process), in line with the classification of pain in the literature (Turk & Melzack, 2001).

Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (International Association for the Study of Pain, 1994). This definition highlights that pain is a multifactorial experience, involving biological, psychological and sociocultural factors (Turk, 1996). This biopsychosocial understanding of pain challenges the purely biomedical explanation of pain which was dominant until the 1960s for pain conditions in general. Although before this time psychological factors were considered for understanding chronic pain, pain was viewed as having *either* biological *or* psychological causes (Turk & Monarch, 2006). Biopsychosocial models, however, suggest that pain is experienced as a result of complex and dynamic interactions between biological, psychological and social factors, rather than simply being caused by physiological damage to a particular body site, as proposed by medical explanations (Turk, 1996). The most prevalent biopsychosocial understanding of pain is the gate control theory (Melzack & Wall, 1965).

The gate control theory proposes that the experience of pain is modulated by a chemical ‘gate’ in the dorsal horn of the spinal cord, located in between the body site and the brain. In the theory, this ‘gate’ can be opened or closed depending on whether excitatory or inhibitory fibres are stimulated. The theory’s biopsychosocial nature is that it proposes that inhibition or excitation of pain signals can occur at both a ‘bottom-up’ sensory level in terms of nerve activity (the biological element) from the peripheral body site, but also at a ‘top-down’ level in terms of the role of the brain on the pain gate. The concept of this ‘top-down’ process suggests that psychological factors such as mood and attention are involved in the excitation or inhibition of fibres at the pain gate (Turk & Monarch, 2006). Although the gate control theory has been criticised for a lack of evidence for its physiological aspects, it has remained an influential biopsychosocial theory of pain and led to increased interest in the role of psychosocial factors in the experience of pain (Turk & Monarch, 2006). The gate control theory has also been developed further into the neuromatrix theory, which includes more details regarding the neural networks in the brain involved in the experience of pain (Melzack, 2005).

The assessment of pain is a complex area, and an extensive range of methods and tools exist (Turk & Melzack, 2001). The majority of assessment tools used in both research and clinical practice are unidimensional measures of pain *intensity* (i.e. the perceived strength of the pain) (Turk & Melzack, 2001). Rating scales of pain intensity (such as an NRS or VAS), require the individual to indicate the level of their pain in a specified time period on a linear scale (Jensen & Karoly, 2001). These tools are easily administered and are thought to have good construct validity (Jensen & Karoly, 2001). However, they have been criticised for only measuring the sensory component of pain and not capturing information regarding other pain dimensions, such as psychological aspects of the experience in terms of emotional and cognitive components (Huber et al., 2007; Jensen & Karoly, 2001). Multidimensional pain questionnaires have been developed to enable assessment of more than just the intensity of the pain, such as the McGill Pain Questionnaire (Melzack, 1975) and the ICOAP (a measure specific to hip or knee OA; Hawker et al., 2008). However, although these multidimensional tools are able to measure a range of the relevant pain dimensions (and are therefore more comprehensive than unidimensional rating scales), they cannot identify the underlying pain mechanism (Scholz & Woolf, 2002). Identification of underlying pain mechanisms is a key interest in knee OA research in terms of identifying subgroups of patients and targeting interventions according to this phenotyping (Phillips & Clauw, 2011).

It appears important to be able to identify the pain mechanism in chronic pain conditions such as knee OA, as the process of central sensitisation is thought to be involved for at least some patients.[1] In the case of knee OA, it is only recently that the dominant understanding of pain being due to mechanical knee damage (and therefore *via* peripheral and nociceptive mechanisms) has been challenged by suggestions that central sensitisation is also involved (Harden et al., 2013; Phillips & Clauw, 2011; Woolf, 2011). Pain due to central sensitisation or a combination of peripheral nociception and central processes is thought to be less responsive to traditional medical treatments (i.e. medication and surgery) and

[1] I recognise that 'central sensitisation' is not a proven concept in knee OA, and that QST data may not measure central pain processing. However, as central sensitisation is a key theory within the QST literature, it was deemed important to include it within this thesis.

psychological interventions have been advocated for patients with central sensitisation (Phillips & Clauw, 2011). QST is considered an appropriate method of assessing central sensitisation in knee OA (Courtney, Kavchak, Lowry, & O'Hearn, 2010; Hochman, Davis, Elkayam, Gagliese, & Hawker, 2013). QST is currently only used in research, although it has been suggested that the methodology could be beneficial in clinical practice (Fillingim, 2005; Pavlaković & Petzke, 2010) in terms of indicating which patients could benefit from interventions other than traditional medical treatments aimed at reducing peripheral nociceptive pain (Phillips & Clauw, 2011).

The main explanation for central sensitisation in knee OA in the literature is that it develops from ongoing and prolonged peripheral nociception (Courtney et al., 2010). It has also been suggested that individuals may have a genetic predisposition to develop central pain sensitivity difficulties (Phillips & Clauw, 2011). A further proposed explanation of central sensitisation is that psychosocial factors (such as increased levels of depression and anxiety, and 'unhelpful' cognitions and behaviour; Vranceanu, Barsky, & Ring, 2009) may be involved in its development (Courtney et al., 2010), although this has received minimal attention in the literature, particularly for peripheral musculoskeletal diseases such as knee OA.

Similarly, as with explanatory models for central sensitisation in knee OA, models of pain in the condition generally remain much more dominated by a biomedical understanding (e.g. Harden et al., 2013) than for some other painful conditions such as low back pain. This might be linked to the presence of a commonly-used surgical procedure for knee OA (knee replacement surgery) but not for many other pain conditions, as well as the minimal focus of pain in the OA literature generally (Jordan & Gracely, 2013). However, the research base in knee OA is beginning to address this, and a biopsychosocial understanding of the condition has been advocated in the literature (Hunt, Birmingham, Skarakis-Doyle, & Vandervoort, 2008). For example, a biopsychosocial framework of knee OA has enabled researchers to develop hypotheses for the common (and difficult-to-explain within a solely medical model) finding that radiographic damage of the knee (damage shown by x-rays or other medical scans) is not always strongly

associated with level of pain reported by knee OA patients (e.g. Bedson & Croft, 2008).

For example, in a recent study which separated knee OA patients into subgroups according to whether they had high or low levels of self-reported pain and high or low radiographic knee damage, Finan, Buenaver, et al. (2013) found significantly higher levels of depression and anxiety reported by patients in the high pain/low radiographic damage group compared to those in the low pain/high radiographic damage group. This highlights the importance of considering psychosocial factors alongside biological factors in understanding the experience of pain in knee OA. Finan et al.'s findings suggest that anxiety and depression may have key roles in the experience of pain for patients with knee OA, and that these factors may help explain (at least some of) the discrepancy in patients with high levels of reported pain but minimal knee damage.

Higher levels of depression and anxiety have been found to be associated with higher reported pain by people with knee OA (e.g. Salaffi, Cavalieri, Nolli, & Ferraccioli, 1991; Summers, Haley, Reveille, & Alarcón, 1988). These studies found that both depression and anxiety (as measured by self-report questionnaires) were positively correlated with different aspects of pain (including sensory and affective pain components), meaning that higher levels of depression and anxiety were associated with higher self-reported pain. However, the Salaffi et al. study found higher correlations (with *r*-values of approximately .6) than the Summers et al. research (*r*-values of approximately .3), which highlights that mood may not have a consistent impact on pain in knee OA, and that other factors may be involved.

Depression and anxiety have also been found to be associated with QST data (thought to quantify the level of central sensitisation; Courtney et al., 2010) in knee OA (e.g. Finan, Buenaver, et al., 2013). This study found negative correlations of approximately $r = -.3$ between both depression and QST data, and anxiety and QST data. These findings suggest that lower QST values (which suggest more pain sensitivity and greater central sensitisation) are associated with higher levels of depression and anxiety. This is in line with the central

sensitisation literature in which psychological factors are thought to be involved in the development of central pain processing, and in the transition from peripheral nociceptive mechanism to either a mixed central/peripheral process or one defined by central processing (Courtney et al., 2010).

Although the cognitive-behavioural fear-avoidance model (Lethem, Slade, Troup, & Bentley, 1983) is arguably the most prevalent psychological theoretical explanation of the link between mood and pain it has several limitations (Pincus, Smeets, Simmonds, & Sullivan, 2010). The fear-avoidance model does provide an explanation for how anxiety, depression, and further pain can develop following the onset of pain, in terms of its proposal that individuals may engage in behavioural avoidance of the feared experience (i.e. pain) by disengaging from physical activity, but that this can then result in further pain and the development of depressed mood. However, it has been described as overly-simplistic, and criticised for focussing more on the experience of fear, when it could be argued that avoidance of activity is the key factor involved in the development and maintenance of mood difficulties in the context of pain, rather than anxiety being the key factor (Moseley, 2011; Pincus, Vogel, Burton, Santos, & Field, 2006). Furthermore, the fear-avoidance model does not provide an explanation of why some people experience anxiety at the onset of pain, and some do not, which is a common criticism of cognitive-behavioural theory more generally. Also, the model proposes that depression and anxiety are responses to pain, whereas it has been suggested that some patients experience depression prior to pain onset, and that the depressive symptoms can lead to increased behavioural avoidance, which can lead to increased pain and disability (Pincus et al., 2010; Pincus et al., 2006). Some of these criticisms lead Pincus and colleagues to update the fear-avoidance model to account for some of its shortcomings. The updated model includes a ‘social beliefs pathway’, in which attempted avoidance of pain can be due to the individual’s social and cultural context and the beliefs regarding pain and health within this context (Pincus et al., 2006). The extended fear-avoidance model also includes a ‘depression pathway’, which proposes that depression before injury and the onset of pain can result in further pain and disability with or without the involvement of fear (Pincus et al., 2006). In the existing central sensitisation literature, psychological theories have seldom been

applied to this pain process. However, George, Wittmer, Fillingim, and Robinson (2007) applied the fear-avoidance model to a QST study with low back pain patients. As increased depression, anxiety and/or avoidance are thought to lead to worsened pain in (all forms of) the fear-avoidance model, it means that the model could account for central sensitisation, as prolonged nociception is thought to be involved in the development of this central pain process (Courtney et al., 2010). Therefore, applications of the fear-avoidance model to central sensitisation are likely to frame depression and anxiety as having causative status.

Linked to the depression pathway within the Pincus et al. (2006) updated fear-avoidance model, in a discussion regarding a cognitive-behavioural diathesis-stress framework regarding the link between depression and chronic pain, Banks and Kerns (1996) present three potential relationships between depression and chronic pain: 1. Depression may precede chronic pain; 2. The two difficulties may begin simultaneously; or 3. Depression begins as a reaction to experiencing pain. Banks and Kerns (1996) then go on to introduce a diathesis-stress model, which they propose explains each of these three scenarios. In their diathesis-stress framework, a proportion of individuals are thought to have a vulnerability to depressive mood (be that at a behavioural, cognitive or biological level). The authors suggest that pain then acts as a stressor, and for those patients with a vulnerability to depression, pain can either trigger low mood and avoidance behaviour or exacerbate existing depressive symptomatology (Banks & Kerns, 1996). Although this framework does not explicitly apply itself to central sensitisation, it could account for the role of depression in central sensitisation for the group of patients who are depressed prior to the onset of pain. The authors suggest that depression can lead individuals to pay more attention to bodily sensations and that this can lead to increased sensitivity to pain thresholds and tolerance (Banks & Kerns, 1996) (which are now thought to be constructs linked to central sensitisation; Courtney et al., 2010, and could lead to a chronic pain state). Therefore, similarly to the fear-avoidance model, the diathesis-stress model suggests that depression can cause the development of central sensitisation, *via* a vulnerability to engage in hypervigilant behaviour and experience unhelpful cognitions (Banks & Kerns, 1996).

Another key model in terms of understanding the pain-depression relationship is enmeshment theory (Pincus & Morley, 2001), which is more cognitively-focussed than the fear-avoidance or diathesis-stress models. Enmeshment theory suggests that for some individuals, pain and illness beliefs are 'enmeshed' or attached to their beliefs regarding their self-identity, both in terms of who they are now and who they could be in the future (Morley, Davies, & Barton, 2005; Sutherland & Morley, 2008). The model proposes that when all three types of cognition (i.e. beliefs regarding pain, illness, and self-identity) are enmeshed, this can lead to greater depression and disability (Pincus & Morley, 2001). Enmeshment theory suggests that depression can occur before or following the onset of pain, and it also draws on some of the vulnerability ideas from diathesis-stress frameworks, in terms of some individuals having a vulnerability to experience low mood in response to pain, although this vulnerability is described as much more linked to cognitive biases in the enmeshment model (Pincus & Morley, 2001). Although the model focusses on the role of depression in chronic pain, it does propose that anxiety may be involved if the individual is fearful of their perceived future-self (Sutherland & Morley, 2008). Enmeshment theory does not appear to easily apply to central sensitisation, although it could be that if enmeshment of beliefs regarding pain, illness, and the self lead to greater depression and disability (including increased pain; Pincus & Morley, 2001), then this increased pain could develop to central sensitisation (Courtney et al., 2010). Therefore, again, this psychological theory could be interpreted to suggest that depression is involved in the cause and development of central processes in chronic pain.

The final psychological model of the mood-pain relationship that it is important to introduce is the pain acceptance model (McCracken, 1998), an acceptance and commitment theory (Hayes, Luoma, Bond, Masuda, & Lillis, 2006). This theory suggests that if an individual does not accept their experience of pain and tries to avoid it, they will miss out on valuable and meaningful life experiences, have a greater risk of experiencing anxiety and depression, and generally have a lower level of overall functioning (McCracken, 1998; McCracken & Eccleston, 2003). The role of chronic pain acceptance could be involved in the development of

central sensitisation (and its relationship to depression and anxiety) in a similar manner as discussed for the other psychological models above. Specifically, patients with low levels of pain acceptance are more likely to engage in behavioural avoidance of pain (e.g. disengagement from physical activities), which, as well as having a negative effect on mood, is likely to lead to decreased use of the damaged body site (e.g. the knee in knee OA) and increased pain (McCracken & Eccleston, 2003). So, as discussed previously, this increased nociception could then cause central sensitisation mechanisms to develop (Courtney et al., 2010). However, acceptance could also provide a hypothesis of central sensitisation leading to depression and anxiety. If an individual is highly accepting of experiencing pain and has high pain sensitivity, then it would make sense that increased experience of pain (at a central level) would trigger less distress (depression and anxiety) than for someone with low pain acceptance and high central sensitisation. Therefore, the acceptance model could provide an understanding of a reciprocal relationship between depression/anxiety and central sensitisation.

This background has presented details of the limited existing literature regarding the role of depression and anxiety in central sensitisation in knee OA. The literature review highlights that although, in principle, psychological models could explain the suggested relationship between mood and central sensitisation in knee OA, there is minimal research to enable meaningful inclusion of central sensitisation within existing psychological theories regarding the pain-mood link. Therefore, this thesis research aimed to investigate the relationships between QST data (as a potential measure of central sensitisation), reported pain, depression, and anxiety for people with knee OA.

This is an important area of Clinical Psychology for several reasons. Firstly, the British Psychological Society (2008) has highlighted the importance of Clinical Psychologists working clinically with people with chronic pain conditions (such as knee OA), in terms of providing a psychological aspect to the team's assessment and intervention for each patient. Therefore, with regards to research into assessment methods of pain in knee OA, it appears important that Clinical Psychological theory and understanding is involved so that the evidence base is

not purely medical and that findings regarding mood, for example, are interpreted from a psychological perspective. This is particularly important given the suggestion by Phillips and Clauw (2011) that QST could be used to identify a subgroup of patients who may benefit from additional non-medical interventions, such as psychological therapy. If this is the direction of travel for QST in painful disorders such as knee OA, then it is crucial that psychologists are involved in QST research from the early stages to provide a psychological understanding to how QST is used and to what factors QST data are associated with. Secondly, despite the political drive for Clinical Psychology provision for chronic pain patients within multidisciplinary teams, Clinical Psychologists appear to only be involved in a small proportion of the knee OA research base. This means that, without more psychologically-informed research, the evidence base regarding clinical assessment and intervention of knee OA is likely to remain extremely medical and to not reflect many of the clinical services being provided to people with the condition.

This main aim of the thesis research was addressed *via* three studies, and background information specifically-related to each of these sub-studies is provided below.

1.1. Study 1: An Investigation into the Associations Between PPTs and Self-Reported Pain, Depression, Anxiety, and Demographic Factors in Knee OA

There are different types of QST which induce pain using different stimuli (e.g. pressure, heat, cold, electrical, chemical; Suokas et al., 2012), although pressure QST has been found to have the best test-retest reliability for people with knee OA (Wylde, Palmer, Learmonth, & Dieppe, 2011). As pressure QST is easier and less invasive to administer than some forms of QST (such as chemical QST), it is frequently used in knee OA pain research (e.g. Finan, Buenaver, et al., 2013; Hochman et al., 2013). QST can also be used to measure different constructs including pain thresholds (the minimum amount of stimulus required to induce pain), pain tolerance (how much pain stimuli the person can endure), and pain wind-up effects (multiple ratings of pain in response to repeated application of painful stimuli) (Rolke et al., 2006).

There are two main QST algorithms: the method of limits and the method of levels (Hansson, Backonja, & Bouhassira, 2007). The method of limits involves the level of a stimulus steadily increasing or decreasing until the perceived sensation changes (at which point they alert the person administering the QST who ends the procedure) (Hansson et al., 2007). The method of levels, however, involves the application of a predefined level of stimulus and requires the person to indicate whether they can perceive the stimulus or whether it is painful (depending on the focus of the QST) (Hansson et al., 2007). According to Hansson and colleagues, the method of limits form of QST is used more frequently due to the time-consuming nature of the method of levels.

As well as the research which suggests a relationship between depression/anxiety and QST data in knee OA (Finan, Buenaver, et al., 2013), significant associations have also been found between QST values and self-reported pain. For example, Arendt-Nielsen et al. (2010) found a significant correlation (r = -.24) between self-reported pain (as measured on a VAS unidimensional tool) and PPT in a knee OA sample. This finding suggests that lower PPTs (i.e. more pain sensitisation) are associated with higher levels of subjective pain. The finding of a small correlation suggests that QST and subjective pain ratings do not measure identical constructs, which could provide evidence for the suggestion in the literature that QST measures central sensitisation (Courtney et al., 2010) and self-report measures often measure pain intensity without the ability to identify the underlying mechanism for this (Jensen & Karoly, 2001).

The link between demographic characteristics and both self-reported pain and QST-assessed sensitisation has also been researched fairly extensively (Fillingim, 2005). The main demographic factor in the pain literature is gender, with women being frequently found to report higher levels of pain than men on self-report scales (e.g. Fillingim, 2000). Similarly, women have been found to demonstrate lower pain sensitivity than men in QST studies (Chesterton, Barlas, Foster, Baxter, & Wright, 2003; Racine et al., 2012; Riley III, Robinson, Wise, Myers, & Fillingim, 1998), although this finding has not always been replicated in

knee OA samples (e.g. France et al., 2004, who found similar levels of pain thresholds in male and female knee OA patients). Differences in self-reported pain and QST-assessed pain sensitivity have also been found between different ethnic groups, and different age groups (with higher pain/sensitivity in older compared to younger individuals) (Fillingim, 2005).

Aim.

Based on this literature review, Study 1 aimed to investigate the amount of variation in PPTs accounted for by the key factors from the knee OA literature base: self-reported pain; depression; anxiety; and gender. The inclusion of other demographic factors (e.g. age) was considered, but gender is the key demographic factor from the literature and, given that the majority of knee OA begins during older adulthood, a sample of knee OA patients is unlikely to include much variation in terms of age.

1.2. Study 2: An Investigation into the Inter-Rater Reliability of Pressure Algometry QST

The inter-rater reliability of QST is important to consider for several reasons. The QST procedure is fairly time-intensive, and therefore, for pragmatic reasons within research studies, it is likely that multiple people will often have to be involved in undertaking the QST. Although QST has been referred to as 'semi-objective' (May & Serpell, 2009), it is dependent on the application technique of the tester and on the ability of the participant to provide a consistent response regarding their PPT level (Chesterton, Sim, Wright, & Foster, 2007). This means that variability in PPT data could be due to either or both of the following reasons: 1. Inconsistency in the application of the QST by the tester (observer error); or 2. Unreliable responses by the participant (participant error) (Chesterton et al., 2007). As observer error could vary amongst testers, it is important that inter-rater reliability is investigated for QST studies with multiple testers.

For QST using PPT algometry, previous research has identified the rate of applied pressure as the main potential source of measurement error (difference

between the PPT data collected and the 'true value') (Nussbaum & Downes, 1998). This means that if the tester is unable to apply a constant increasing rate of pressure during the testing, this could introduce error into the data and the validity of the measure could be affected. The angle at which the QST is applied has also been highlighted as an important factor which could impact on both measurement error and the ability of the participant to consistently report the PPT level (Greenspan & McGillis, 1994).

The inter-rater reliability of QST also has implications for how useful the procedure could be in clinical settings. It has been suggested that QST could be used in clinical practice as an assessment tool or outcome measure (Fillingim, 2005; Pavlaković & Petzke, 2010). It is therefore of paramount importance that the tool is reliable and consistent when administered by different personnel. For instance, if the methodology is prone to poor inter-rater reliability, it could be that patient scores could not be compared to those of other patients tested by different personnel, or that change over time for an individual patient could only be reliably monitored if the QST measurements were collected by the same person over time.

Previous studies have investigated the inter-rater reliability of QST measuring PPTS, such as Chesterton et al. (2007), who found good inter-rater reliability. However, this study used fixed-angle pressure algometry, and so it is possible that more variation could have been present in the QST methodology of this thesis research as the angle was dependent on the person applying the tool.

Aim.

Therefore, the aim of Study 2 was to establish whether there was an acceptable level of inter-rater reliability between the two testers who administered the QST in this thesis research. The reason for conducting this sub-study was to provide further information of the assessment tools used in the main study (Study 1) to inform the interpretation of the study findings.

1.3. Study 3: Rasch Analysis of the STAI-SF

The STAI-SF (Marteau & Bekker, 1992) is a six-item measure of anxiety. It requires the respondent to indicate the extent to which each item (e.g. *I feel calm*) describes them on a four-point Likert scale (where 1 refers to 'not at all', 2 refers to 'somewhat', 3 refers to 'moderately', and 4 refers to 'very much'). The possible total STAI-SF score ranges from 4 to 24, with higher scores indicating higher levels of anxiety. The STAI-SF was developed from the full-length 40-item STAI (form Y) measure, which is composed of 20 items measuring state anxiety and 20 items measuring trait anxiety (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). State anxiety is defined as a fear or worry induced by a situation perceived as threatening in some way, which is transient in nature, whereas trait anxiety is thought to be a more stable level of fear or worry that occurs across a range of non-threatening everyday situations (McDowell, 2006; Spielberger & Sydeman, 1994).

The STAI-SF includes half of the 'state anxiety' items from the full-length STAI (form Y) and none of the 'trait anxiety' measures (Marteau & Bekker, 1992). Previous pain research has also excluded trait anxiety items of the STAI (e.g. Berman, Iris, Bode, & Drengenberg, 2009; Robinson, Bialosky, Bishop, Price, & George, 2010), based on the argument that state anxiety is a more relevant construct that trait anxiety in such studies (Robinson et al., 2010). Another six-item version of the STAI was developed by Chlan, Savik, and Weinert (2003), which has only one item in common with Marteau and Bekker's version. In a comparison of both six-item versions of the STAI, Tluczek, Henriques, and Brown (2009) observed that the Marteau and Bekker STAI version is more focussed on cognitive and anticipatory aspects of anxiety than the Chlan et al. version, which focusses more on the somatic experience of anxiety. Therefore, it appears that the Marteau and Bekker (1992) STAI-SF is more appropriate for use with knee OA patients than the Chlan et al. version for several reasons. Anxiety-related cognitive factors have been found to be important in the experience of chronic pain, such as that usually experienced in knee OA, including fear-avoidance beliefs (Waddell, Newton, Henderson, Somerville, & Main, 1993) and pain catastrophising (i.e. exaggerated beliefs regarding the individual's pain

experience and their ability to cope with this both currently and in the future; Keefe, Brown, Wallston, & Caldwell, 1989).

Linked to these cognitive factors, a qualitative study conducted by Pouli, das Nair, Lincoln, and Walsh (2014) with people with knee OA found that fear regarding the future (a form of anticipatory anxiety) was an important aspect of the experience of living with the condition. Anxiety-related cognitive features are also central to the fear-avoidance model of chronic pain (Lethem et al., 1983; see earlier in the Extended Background). Based on these reasons, the Marteau and Bekker (1992) STAI-SF appears an appropriate measure to assess anxiety in people with knee OA, and, arguably, more appropriate than the Chlan et al. (2003) version.

The STAI, in its numerous forms, is highly used in both research and clinical practice, and McDowell (2006) described it as “one of the best measures of anxiety available” (p.325). Versions of the STAI have been used in studies investigating the correlational relationships between pain and psychological factors both in knee OA patients (e.g. Finan, Buenaver, et al., 2013; Study 1 of this thesis) and in patients with other musculoskeletal conditions (e.g. Valencia, Fillingim, & George, 2011). Versions of the STAI have also been used in research which aimed to identify subgroups of knee OA patients (such as those with high reported pain levels but low radiological knee damage) in order to develop an understanding of the assessment and treatment needs of the patients in these subgroups in clinical practice (e.g. Finan, Buenaver, et al., 2013; Williams et al., 2004). Therefore, due to the use of the STAI-SF in correlational and subgroup research with knee OA patients, it is important to ascertain the psychometric utility of the STAI-SF with this client group in order to critically evaluate the findings of such research. If the STAI-SF was not found to be an appropriate measure of anxiety for people with knee OA, then it could lead to difficulties in drawing conclusions about the relationships between anxiety and other factors in research using the STAI-SF.

The STAI-SF is also often used to evaluate treatments in knee OA, including psychological interventions, in order to investigate whether the intervention

resulted in any significant change in participants' anxiety levels (e.g. Berman et al., 2009). Increasing attention is being paid to the utility of psychological interventions with chronic pain patients, including those with knee OA (e.g. Wetherell et al., 2011). A common aim of these psychological interventions is to reduce patients' anxiety levels (Roditi & Robinson, 2011), which is important as it has been suggested that high levels of anxiety may lead to increased maladaptive reactions (such as avoidance) to the physical symptoms of OA and to worsening of OA pathology (McWilliams, Goodwin, & Cox, 2004). As with the use of the STAI-SF in correlational and subgroup research, it is crucial to investigate the psychometric properties of the measure so that the STAI-SF results regarding the efficacy of psychological interventions can be interpreted alongside an understanding of its psychometric utility with knee OA patients.

The psychometric properties of the STAI-SF have been investigated in a wide range of populations (Marteau & Bekker, 1992; Tluczek et al., 2009), including chronic pain samples (Berman et al., 2009). These studies found the STAI-SF to have acceptable (≥ .7) to good internal consistency (≥ .8) (Kline, 1999), with Cronbach's α values ranging from .79 to .85. Construct validity of the STAI-SF has also been shown (Court, Greenland, & Margrain, 2010; Marteau & Bekker, 1992; Tluczek et al., 2009). Although test-retest reliability is often reported for questionnaire measures, it is arguably not an important characteristic for the STAI-SF to demonstrate due to the transient and situation-specific nature of state anxiety (Marteau & Bekker, 1992).

Rasch model and analysis.

The STAI-SF, like many questionnaire measures, was developed using the standards of reliability and validity (Marteau & Bekker, 1992). These standards are based on Classical Test Theory, which, although useful, is now being complemented by more modern psychometric models, such as the Rasch model (Pallant & Tennant, 2007). The Rasch model (Rasch, 1960) proposes that the probability of a particular person responding highly to a questionnaire item is a function of the distance between the individual respondent's 'ability level' (i.e. how much of the construct being measured they have) and the 'difficulty level' of the

questionnaire item (i.e. whether a high score on the item indicates a high level of the construct being measured). In the case of a questionnaire measuring anxiety (such as the STAI-SF), the Rasch model would propose that the probability of an individual responding highly to one of the items would depend on both the person's level of anxiety and the level of anxiety communicated by the questionnaire item (Pallant & Tennant, 2007).

Another aspect of the Rasch model is that the questionnaire should work in the same regardless of what subgroup the participant belongs to (Tennant & Conaghan, 2007). This means that males and females, or people of different (pre-determined) age groups should have the same probability of responding highly to each questionnaire item, if they have the same level of the construct (e.g. anxiety) (Pallant & Tennant, 2007). If items of a measure work in different ways for different subgroups of a sample (e.g. based on gender or age), then the questionnaire is said to show *differential item functioning* (DIF; Tennant & Conaghan, 2007).

Rasch analysis is based on the Rasch model, and is thought to offer additional information regarding the psychometric properties of an ordinal or interval level scale (Tennant & Conaghan, 2007). Rasch analysis enables researchers to investigate the extent to which a sample's responses to a questionnaire measure fit the Rasch model (Pallant & Tennant, 2007). Rasch analysis also assesses whether the scale (e.g. the STAI-SF) is unidimensional (Tennant & Pallant, 2006), which is a characteristic linked to construct validity (Tennant & Conaghan, 2007). A questionnaire is said to be unidimensional if it measures only one construct (such as state anxiety), as the STAI-SF claims to be (Marteau & Bekker, 1992). If there is fit to the Rasch model, Rasch analysis allows ordinal questionnaire data (as in the case of STAIF-SF data) to be transformed to interval level data, which means that change scores could be calculated (Tennant & Conaghan, 2007). This clearly has benefits for using the measure in longitudinal or intervention research.

Rasch analysis and the STAI-SF.

The STAI-SF has not previously been evaluated using Rasch analysis for a knee OA sample, although a literature search found one study which Rasch analysed the STAI-SF for a sample of patients who attended a primary care General Practice in the United Kingdom (Court et al., 2010). However, as different groups of people may respond differently to questionnaire measures, it is important that psychometric analyses are conducted for specific groups.

Indeed the Court et al. Rasch analysis study may not apply to the use of the STAI-SF with knee OA patients. Firstly, participants were recruited from patients attending a general practice who were aged 16 or over, and the mean age of the sample used for the Rasch analysis was 44.4 years. The mean age of this sample is therefore younger than the most common minimum age of diagnosis of knee OA (45 years; Peat et al., 2001). This means that the average age of the Court sample is likely to be around the youngest age in a knee OA sample. Secondly, the Court study used age subgroups of <50 and ≥50 to investigate any response differences between these age groups. However, the majority of knee OA patients would fall into the ≥50 age group, and so it is not possible to generalise Court's findings of no item DIF for age group on the STAI-SF to the responses between age subgroups in knee OA samples. Thirdly, in the Court study 20% of the participants were attending the health service for an emergency appointment, which is unlikely to apply to most interactions a knee OA patient would have with their GP regarding their condition. Fourthly, the authors of the Court et al. (2010) paper conclude that their Rasch analysis of the STAI-SF suggests that the questionnaire is a valid measure of anxiety in *primary care general medical practice*. Although a proportion of knee OA patients are managed in primary care, a significant proportion are managed in secondary care services, such as those awaiting total knee replacement surgery. Finally, Court's Rasch analysis used the rating scale model version, and so the findings may not apply to STAI-SF data from samples which do not meet the requirements for this version and which instead require the use of the partial credit model version of Rasch analysis. Therefore, based on these differences, it would not be advisable to rely solely on

the information provided by Court and colleagues when considering the psychometric utility of the STAI-SF with knee OA patients.

Although a larger number of studies have used Rasch analysis to evaluate different full-length versions of the STAI (e.g. Davey, Harley, & Elliott, 2013; Kaipper, Chachamovich, Hidalgo, da Silva Torres, & Caumo, 2010; Tenenbaum, Furst, & Weingarten, 1985; Tenenbaum & Furst, 1985), the Rasch analysis of the STAI-SF by Court et al. (2010) suggests that the STAI-SF has different Rasch properties than other versions of the STAI. This suggests that it may not be appropriate to base judgements regarding the psychometric properties of the STAI-SF on the Rasch analyses of other STAI versions.

Aim.

Therefore, Study 3 of this thesis aimed to use Rasch analysis to evaluate psychometric properties of the STAI-SF in a sample of knee OA patients. The main reason for conducting this sub-study was to provide further information of the assessment tools used in the main study (sub-study 1) to inform the interpretation of the study findings.

B. Extended Methods

This extended methods section will include further details of the methodology of Study 1, and details of the methodology for Studies 2 and 3.

2.1. Study 1: An Investigation into the Associations between PPTs and Self-Reported Pain, Depression, Anxiety, and Demographic Factors in Knee OA

Ethical considerations.

See Appendix 2 for my letter of access regarding my involvement in the research and for an email from the Trent Comprehensive Local Research Network confirming what was needed for me to become involved in the project. See Appendix 3 for the ethical approval documentation relevant to study 1 of this thesis (please note: aspects of these documents relate to parts of the wider study that the current research is situated within and so are not relevant to this thesis. However, as ethical approval was granted regarding the full wider project, it is not possible to separate out the documents).

The key ethical issue considered as part of this research was harm to participants, particularly due to the use of QST. As the QST measured pain thresholds rather than tolerance, the algometer was removed as soon as the participant indicated that the pressure stimulus had changed to a painful stimulus. The pain was short-term and participants were able to end participation at any point. These ethical measures are in line with guidance regarding the use of painful stimuli in research with humans (International Association for the Study of Pain, 2013), which state “stimuli should never exceed a subject's tolerance limit and subjects should be able to escape or terminate a painful stimulus at will”. In the current research, pain *thresholds* and not tolerance were measured, and the administration of the painful stimuli was ended immediately once the participant indicated that their PPT had been reached or once they indicated that they wanted the QST stimuli to end for any other reason. Linked to this ethical consideration, informed consent was key. Participants were provided with a participant information sheet (see Appendix 4) and verbal explanation of the QST

procedure (see Appendix 5), before completing a written consent form (see Appendix 6) if they wished to participate in the study.

In terms of the management of harm regarding the questionnaire measures, if a participant scored highly on the BDI-II (particularly on the item assessing suicidal ideation) or expressed severe depression, distress or suicidality during any part of the research process, the Arthritis Research UK Pain Centre's Standard Operating Procedures would have been implemented. However, this procedure did not have to be implemented during my involvement with the research.

Sample size.

G*Power 3.1 software (Faul, Erdfelder, Buchner, & Lang, 2009) was used to calculate the required sample size in order to conduct multiple regression analyses with the PPTs as outcome variables. An effect size of 0.15 was used, based on data from a pilot study conducted within the Arthritis Research UK Pain Centre. In this pilot study, 19 participants were included and QST pain thresholds were collected from four body sites. Multiple regression analysis (with depression, anxiety, gender, and age entered[2]), were undertaken for each body site PPT mean. The R^2 values in these regression analyses ranged from .24 to .51. Using the smallest R^2 value of .24 in the effect size (f^2) calculation ($f^2 = R^2 / (1- R^2)$) produces an effect size of .32. This is in the medium effect size range (.15 to .34; Cohen, 1988). The lower end of this effect size range (.15) was used in the sample size calculation for Study 1 in order to be conservative and to err on the side of caution.

The model used to calculate the sample size was an a-priori, linear multiple regression, fixed, R^2 deviation from zero model. The following model parameters were used to calculate the ideal sample size: effect size (f^2) = .15; power = 80%; α = .05; four predictors in each multiple regression model (pain NRS, depression, anxiety, gender)). This sample size calculation showed that 85 participants were

[2] Although age was not entered (and pain NRS was entered) in the multiple regression analyses in Study 1 of this thesis, it was judged that this pilot study provided a reasonable comparison to base the effect size on in order to calculate the required sample size.

required. Although the final sample size for study 1 (*n* = 77) was slightly below this number, it is more than the sample size suggested by the 'rule of thumb' for sample size in multiple regression of 15 participants for each predictor variable (Field, 2009). Using this 'rule of thumb', the minimum required sample size for each multiple regression model in study 1 would have been 60 participants, which the actual sample size of 77 knee OA patients clearly surpasses.

Demographic details.

Participants were asked for demographic details as part of the questionnaire pack, including age and gender. Only necessary demographic information was be collected. These details were recorded in order to assess who the results are generalisable and, in the case of gender, to include in the data analysis as a predictor variable.

Questionnaires.

This research is part of a wider study (yet to be published) which aims to investigate the utility of questionnaires measuring a variety of psychological factors in knee OA patients. As the questionnaire pack was fairly lengthy, it was presented to participants in one of four orders in order to control for any potential order or fatigue effects. Data from the BDI-II (Beck, Steer, & Brown, 1996) and STAI-SF (Marteau & Bekker, 1992) measures in the questionnaire pack was used for the current study. As not all participants who took part in the wider questionnaire study chose to be involved in the QST study, only BDI-II and STAI-SF data from the participants who undertook the QST was included in Study 1 of this thesis.

The STAI-SF has been shown to have adequate psychometric properties in past studies and has been used in knee OA research (see section 1.3 for details of this). Similarly, the BDI-II has also been used in previous knee OA research (e.g. Williams et al., 2004). Harris and D'Eon (2008) investigated the psychometric properties of the BDI-II with chronic pain patients and found excellent internal consistency (≥ .9) (Kline, 1999). Despite some criticism within the pain literature

that the somatic items of the BDI-II overlap too much with the pain experience, based on their psychometric analysis, Harris and D'Eon (2008) suggest that it is appropriate to retain the somatic items and to use the full BDI-II measure with chronic pain samples. Therefore, both the STAI-SF and the BDI-II were considered appropriate measures of anxiety and depression, respectively, in the current study.

As part of study 3 in this thesis, the STAI-SF data was Rasch analysed, but transformed STAI-SF scores were not used in the analysis of study 1. This was because Rasch-transformed scores were not available for the BDI-II (as this was outside the scope of the research included in this thesis) and it was not considered good practice to include a mix of raw and Rasch-transformed scores in the analysis. Furthermore, as the BDI-II data was at ordinal level, having interval-level STAI-SF data (i.e. the Rasch-transformed scores) would still not allow parametric analyses to be used as the BDI-II data would still necessitate non-parametric correlation analyses. Despite the Rasch-transformed STAI-SF data not being used in the analysis of study 1, the findings of the Rasch analysis were used to critically consider the results regarding the STAI-SF in study 1.

Participants who returned the questionnaire pack with missing data were contacted, where possible, by a researcher to recollect the data. However, recollected BDI-II and STAI-SF data were not included in the current research due to concerns that it could invalidate the remit of the questionnaires to measure recent levels of depression and anxiety, respectively. The BDI-II requires participants to complete the measure based on how they have felt in the previous two weeks. The STAI-SF requires participants to complete the questionnaire based on how they feel at the specific moment. Therefore, any missing data collected at a later date would correspond to a different time-point than the rest of the data for that questionnaire.

Pain NRS.

Although there are criticisms that pain intensity NRS measures do not measure different components of pain (such as affective aspects of pain) (Jensen & Karoly,

2001), a 0 to 10 point pain NRS was used in this study as the tool is used in a wide range of pain and musculoskeletal research (Huber et al., 2007), and it is very quick to complete (Jensen & Karoly, 2001), which was important in order to reduce the time burden on the participants during the QST session.

Pain pressure thresholds.

PPTs were measured using pain-pressure algometry QST (using the method of limits) at knee sites (medial and lateral knee joint-line), a distal body site (medial tibia mid-shaft), and a remote body site (sternum). This form of QST has been found to have the best test-retest reliability for people with knee OA (Wylde et al., 2011). Furthermore, the inter-rater reliability of the two individuals administering the QST in this study was investigated as part of this thesis research (see sections 1.2, 2.2, and 3.2 of this Extended Paper).

Recruitment and process.

See Appendix 7 for the protocol for the wider study that this study is part of. Potential participants were identified by designated 'gatekeeper' professionals in each trust involved in the research. These participants were then sent an invitation letter signed by the healthcare professional responsible for their care. Along with this invitation letter, prospective participants were sent a participant information sheet (see Appendix 4), a consent form (see Appendix 6), and the questionnaire pack (which included the BDI-II and STAI-SF measures). A pre-paid envelope was included for participants to return the completed consent form and questionnaire pack if they decided to take part in the study.

On the consent form, participants were asked to indicate whether they wished to participate in the QST part of the study after completing the questionnaires. Those who indicated that they were interested in taking part in the QST aspect of the study were then contacted by telephone by a researcher to answer any questions the participant had and to arrange a mutually-convenient time for the QST session if they still wished to participate. The QST session took place in a

University of Nottingham clinical research room, and participants were reimbursed for travel expenses.

When participants arrived at the research department, they were met by a researcher and shown to the clinical assessment room to undertake the QST. Further information regarding the QST study was provided by the researcher. At the start of this data collection session, the researcher asked participants to rate the pain intensity at their most painful knee over the previous week on a 0-10 pain NRS. The researcher wrote down the participant's pain NRS rating, and then the QST procedure was carried out by the researcher as described previously in this thesis. PPTs were recorded on a paper record form by the researcher.

Duration of participant involvement.

The questionnaire pack was thought to take approximately one hour to complete (as the pack include numerous questionnaires, many of which related to the wider study and were not part of this thesis research). As participants completed the questionnaire pack in their own home, they could respond to the measures at their own pace. The QST testing session also lasted for approximately one hour.

To participants, the sequence of events in Study 1 were as follows:

Phase 1 The participant was approached by a healthcare professional involved in their care and provided with details of the research.

Phase 2 If the participant chose to take part, they completed the consent form and questionnaire pack and returned this to the research team. If the participant indicated that they did not consent to take part in the QST part of the study then their involvement in the research ended.

Phase 3 If the participant consented to take part in the QST part of the study, they were contacted by a researcher to arrange a convenient time to attend the QST session. At this session, the participant was

asked questions about their pain (i.e. the pain NRS) and they then took part in the QST. At this point, the participant's involvement in this thesis research then ended, although there is the possibility that they may be contacted regarding further aspects of the wider study if they consented to this.

2.2. Study 2: An Investigation into the Inter-Rater Reliability of Pressure Algometry QST

Ethical considerations.

This study received favourable ethical approval from Nottingham Research Ethics Committee one (see Appendix 8 for confirmation of ethical approval). As this sub-study used the same QST methodology as Study 1 of this thesis, the same consideration of ethical issues apply to this study as were discussed in section 2.1.

Participants.

For this sub-study, sample size was calculated based on a similar previous QST inter-rater reliability research (Chesterton et al., 2007). As intra-class correlation coefficients (ICCs) were the planned analysis, the sample size was calculated for this (based on Walter, Eliasziw, & Donner, 1998), and was designed to test for an ICC of .9 with a null value of .7 (based on Chesterton et al., 2007). For the sample size calculation, the following model parameters were used: $n = 2$ (i.e. two researchers administering the QST); power = 80%; $\alpha = .05$. From this, it was calculated that 19 participants would be needed, and therefore the sample of 20 participants for sub-study 2 was of adequate size.

Twenty participants were recruited opportunistically by advertising the study to students and staff at the University of Nottingham. Those who indicated an interest in participating were given a participant information sheet and invited to take part in the study. Recruitment ended after twenty participants were consented into the study. Participants were eligible to take part if they were able

to take part in the QST procedure, if they did not have any significant medical or psychiatric conditions that could adversely affect the results, and if they were capable of providing informed consent. Participants screened themselves for study eligibility.

Healthy control participants were used for Study 2 as this study was concerned with the inter-rater reliability of two researchers who collected the PPT data by conducting QST. Therefore, it is not problematic that healthy controls were tested in this study (and not knee OA participants as in Study 1), as the QST data collected in Study 2 was not of specific interest itself, as the focus was on the comparability of PPTs measured by both testers. The aim of Study 2 was to investigate the inter-rater reliability of data collected *via* the QST methodology used in Study 1, and the same researchers administered the QST in both studies. Furthermore, although difference in PPTs between individuals have been found for factors such as gender (e.g. Riley III et al., 1998) and physical health status (Wylde et al., 2011), such characteristics have not been found to impact on the reliability of individual participants' responses in previous QST literature (Chesterton et al., 2007).

Procedure.

See Appendix 9 for the protocol for Study 2. When potential participants indicated they were interested in taking part in this study, they were sent a participant information sheet (see Appendix 10). The study was undertaken in a University of Nottingham clinical research room, and the procedure lasted for approximately 60 minutes per participant. One of two researchers explained the procedure by verbally reiterating the details included in the participant information sheet. Once the researcher had confirmed that the individual was eligible to take part and that they understood the details of the study, the participant provided written consent by signing a consent form (see Appendix 11).

Before starting the QST procedure, participants were asked by a researcher to provide demographic details (gender, age). This information was collected in order for the findings to be placed in the context of the participant sample

characteristics. QST was then undertaken which measured PPTs on the following body sites: nailbed (as a learning site for the participant to understand the procedure), medial knee joint line, lateral knee joint line, medial tibia mid shaft. The same QST procedure was used as in Study One: see section 2.1 for details. QST was undertaken for each participant by two researchers trained in the procedure (the same personnel as in Study One). One researcher conducted the QST procedure, and then the other researcher repeated this testing. There was a five minute break between the first and second QST procedures in an attempt to prevent against any potential pain sensitivity wind-up effects.

To control for any order effects (including any potential impact of repeating the QST procedure), the order of the testers was counterbalanced, using the method of 'complete counterbalancing'. In practice, this meant that one researcher conducted the first QST set for half of the participant sample, and the other researcher conducted the first QST set for the other half of the sample. Participants were assigned an identification (ID) number when they arranged the appointment time for them to take part in the study. The ID numbers were assigned in sequentially increasing order (so the first participant was '1', the second was '2' and so on). Participants assigned with an odd ID number received the QST from Researcher A first and then from Researcher B, whereas those with an even ID number received the QST from Researcher B first and then from Researcher A. Figure 1 illustrates the participants' journey through the study process.

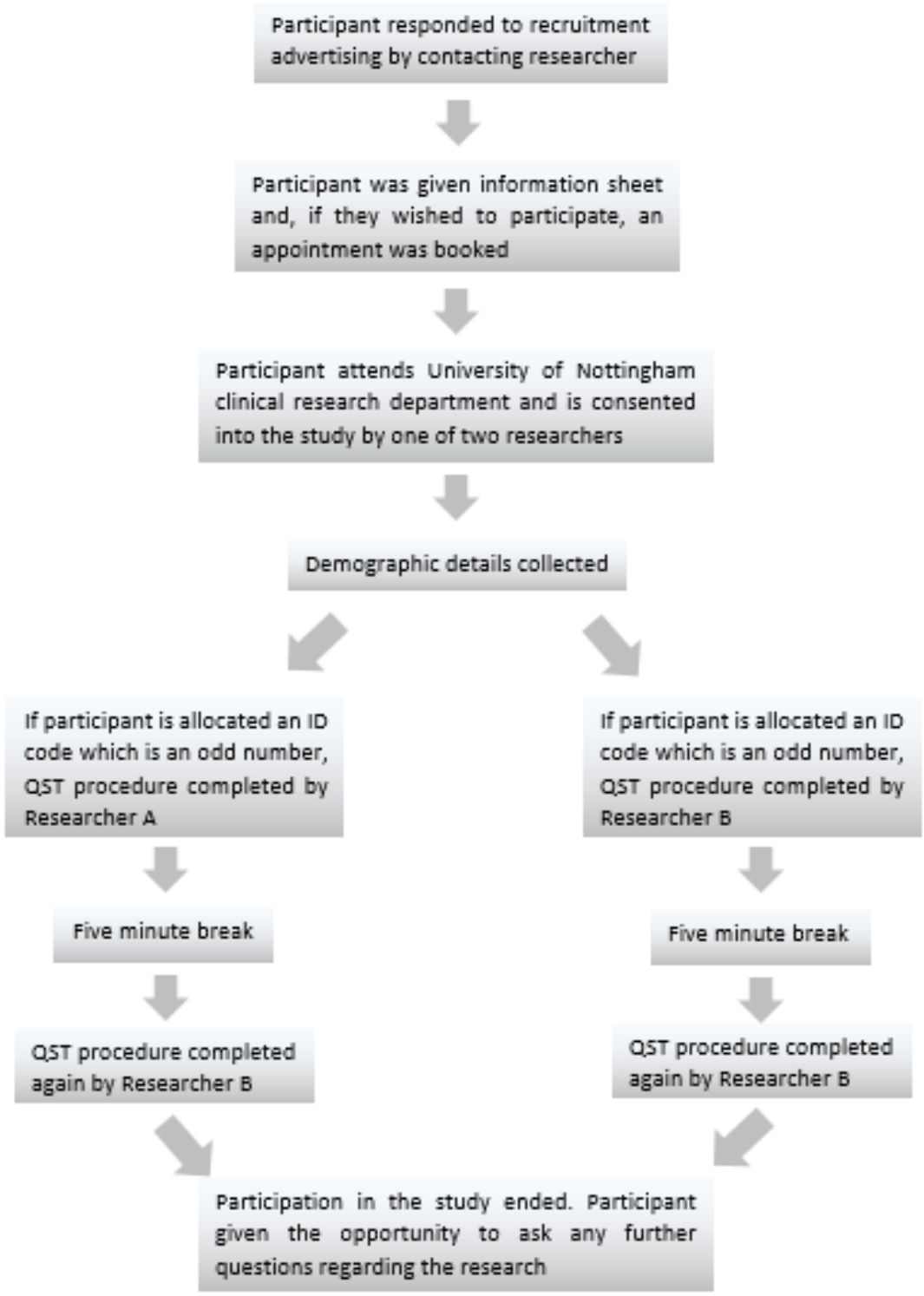

Figure 1. A diagram depicting the study process for Study 2.

Data analysis.

The means and standard deviations were calculated for each of the four QST test sites (sternum, medial and lateral knee joint-lines, and medial tibia mid-shaft; no the nailbed as this was the learning site for the participant, as in Study 1).

The inter-rater reliability for the PPTs at each body site was investigated using ICC analysis. Hallgren (2012) recommends ICC analysis for the investigation of inter-rater reliability, and this method of analysis has been used in previous QST inter-rater reliability research, although not in the majority of these studies (Chesterton et al., 2007). Based on guidance by Hallgren (2012), inter-rater reliability in this sub-study was assessed using two-way mixed, absolute agreement, single measures ICC analysis (McGraw & Wong, 1996). The model was two-way as both researchers conducted the QST for each participant. The model was set as mixed-effects as the aim of this sub-study was to investigate the reliability between two testers rather than to generalise the reliability findings to other testers. In the ICC analysis, good inter-rater reliability was characterised by absolute agreement (rather than relative consistent agreement). As QST is considered within the literature to be an objective measure of pain sensitivity (Courtney et al., 2010), absolute agreement in terms of inter-rater reliability was therefore a suitable analysis parameter. Finally, a single-measures ICC model was used as although all participants in this sub-study were tested by both researchers (which would usually suggest the use of an average-measures ICC model), the aim of Study 2 was to inform the findings of Study 1, in which participants were tested by one of two researchers (and not both as in Study 2) (Hallgren, 2012).

95% Confidence Intervals (CIs) were also calculated for each ICC, in order to allow comment on the variability of the inter-rater reliability. ICCs fall between 0 and 1. The classification system proposed by Cicchetti (1994) was used to categorise the ICC values for the PPTs at each body site. See Table 11 for details of these qualitative labels and their corresponding ICC cut-off values. The Cicchetti (1994) classification system is frequently used in inter-rater reliability research utilising ICCs as a method of data analysis (Hallgren, 2012), and

therefore appears an appropriate method of describing the ICC data in the current research.

Table 11.

Details of the ICC classification system proposed by Cicchetti (1994).

ICC value	Classification
Less than .40	'Poor'
Between .40 and .59	'Fair'
Between .60 and .74	'Good'
Between .75 and 1.0	'Excellent'

2.3. Study 3: Rasch Analysis of the STAI-SF

Ethical considerations.

As this sub-study was part of the same wider research project as Study 1, please see section 2.1 regarding the ethical approval and ethical considerations for the Rasch analysis sub-study.

Participants.

The sample for this aspect of the research consisted of 246 people with a diagnosis of knee OA. The sample size was based on the recommendation for Rasch analysis, which suggests data should be analysed from approximately 250 individuals (Linacre, 1994). These participants were recruited *via* the same recruitment strategy outlined in section 2.1, as the sample for Study 1 were recruited from the sample for this study (Study 3).

Procedure.

As the recruitment and data collection aspects of this Rasch analysis sub-study were identical to those regarding the questionnaire elements of Study 1, these will not be repeated here. The questionnaire pack posted to participants included the STAI-SF (Marteau & Bekker, 1992) and a pain intensity NRS. Participants who returned the questionnaire pack with missing data were contacted, where possible, by a researcher to recollect the data (as part of the protocol for the wider study). However, recollected STAI-SF data are not included in the current research due to concerns that it could invalidate the questionnaire's remit to measure 'state anxiety' (i.e. collecting different items of the STAI-SF on different days could result in data collection regarding anxiety in two different 'states'). As this study focussed on the psychometric properties of the STAI-SF in a knee OA sample, data was analysed from all STAI-SF questionnaires completed by participants in the wider research project with the Arthritis Research UK Pain Centre at the University of Nottingham, regardless of whether they went on to take part in the QST procedure. Therefore, some, but not all, of the participants included in the sample for this sub-study also constituted the sample for Study 1 in this thesis.

Data analysis.

Descriptive statistics were calculated regarding the demographics and pain-level of the sample.

Rasch analysis.

As part of the data preparation stage prior to the completion of Rasch analysis, the internal consistency of the STAI-SF data was evaluated using the Cronbach's alpha statistic. Rasch analysis was carried out using the RUMM2020 software (Andrich, Lyne, Sheridan, & Luo, 2003), and the data was checked for accuracy once it had been entered into RUMM2020. In line with the requirements for Rasch analysis in RUMM2020, the possible responses for each item were changed from '1, 2, 3, or 4' to '0, 1, 2, or 3' (Andrich et al., 2003). To decide whether the rating scale (Andrich, 1978) or partial credit version (Masters, 1982) of the Rasch model should be used, a likelihood ratio test was undertaken. As the likelihood ratio test was significant ($p<.05$), the partial credit Rasch model was used. Each individual item of the STAI-SF was investigated for disordered response thresholds (Pallant & Tennant, 2007; Tennant & Conaghan, 2007). When disorder thresholds were observed for an item, that item was re-scored by collapsing adjacent response options (e.g. 0,1,2,3 could be rescored to 0,1,1,2) (Pallant & Tennant, 2007). Summary statistics were then inspected for the data including the re-scored item, and the rescoring was included in the subsequent Rasch analysis if it resulted in an improved fit to the model (Shea, Tennant, & Pallant, 2009).

Summary statistics in RUMM2020 were analysed as a first step in the Rasch analysis. Fit residual statistics were calculated for both the items and the persons. These fit residuals were transformed to estimate a z-score with normal distribution (Pallant & Tennant, 2007). Therefore, if the item or person showed good fit with the Rasch model, the transformed mean and SD fit residuals should equal 0 and 1 respectively (Pallant & Tennant, 2007). Groups of participants (called 'Class Intervals') were created to separate out the participants with a low or high 'trait ability level' (i.e. anxiety level) (Tennant & Conaghan, 2007). These Class Intervals should be of equal size for each item, including approximately 50 cases per item (Psychometric Laboratory for Health Sciences, 2007). An item-trait interaction Chi-squared analysis was conducted to test whether the hierarchical ordering of all of the STAI-SF items was invariant across different anxiety levels (i.e. the class intervals) (Moreton, Wheeler, Walsh, & Lincoln, 2012; Tennant & Conaghan, 2007). If this statistic was significant ($p < .05$, with

Bonferroni Correction for the number of items), then it can be concluded that the ordering of the items varies across the spectrum for the state anxiety trait (Pallant & Tennant, 2007).

The Person Separation Index (PSI) was calculated as a measure of internal consistency in the STAI-SF data. If the PSI value was 0.7 or above this indicated acceptable internal consistency reliability (Fisher, 1992; Shea et al., 2009). An acceptable PSI value would also suggests that the Fit Statistics produced were reliable without an excessive amount of error.

In the next step of the Rasch analysis, individual items and participants were investigated for misfit to the Rasch model. To examine item-fit, Chi-square and Analysis of Variance (ANOVA) statistics with a Bonferroni correction were used. To investigate the fit for both items and persons, fit residuals were examined, and values between -2.5 and 2.5 were considered to demonstrate acceptable fit to the Rasch model (Moreton et al., 2012; Pallant & Tennant, 2007). If misfit of items and/or persons was found, these would be dealt with by investigating if removal of these improved the overall fit of the STAI-SF data to the Rasch model (Moreton et al., 2012; Psychometric Laboratory for Health Sciences, 2007).

DIF was investigated using an ANOVA with a Bonferroni Correction for the person factors (gender [males and females] and age group [under 65; 65 to 71; 72 and above])[3]. If a questionnaire item shows DIF then this suggests that the item is performing differently for people who fall into different subgroup categories (in this case, gender or age group), even if they have the same level of anxiety.

Local dependency (Baghaei, 2007) of the items in the STAI-SF data was tested by examining how the residuals of each item correlated with that of the other items. If an item is *dependent*, this means that an individual's response to it would

[3] Although there is no specified method of defining the age groups used in Rasch analyses, the age groups used were selected because they each contain approximately equal participant numbers. The 'under 65' group contained 77 participants, and the '65 to 71' and '72 and above' groups both contained 84 participants. Furthermore, the age group split made sense in terms of the 65 years-old age cut-off between 'adult' and 'older adult' that is often used in NHS contexts.

have a direct bearing on their response to another item on the same measure (Baghaei, 2007). A positive correlation of above 0.3 between the residuals of two items would suggest response dependency between those items (Ramp, Khan, Misajon, & Pallant, 2009).

Linked to the concept of local response dependency is unidimensionality (Pallant & Tennant, 2007; Tennant & Pallant, 2006). Unidimensionality was tested for *via* the method outlined by Smith (2002). Principal Components Analysis was run on the residuals to identify two subgroups of items: a set of three items which loaded positively onto the first component and a set of three items which loaded negatively. Independent *t*-tests were then undertaken to look for any differences in the estimated scores for both subgroups of items, and if more than 5% of these *t*-tests were significant (at the $p = .05$ level), then unidimensionality may be breached. If more than 5% of the *t*-tests were significant, a Binomial Confidence Interval would be used to investigate unidimensionality further, and if the lower 95% Confidence Interval proportion was above 0.05 then the measure would be considered non-unidimensionality (i.e. multidimensional) (Shea et al., 2009; Tennant & Pallant, 2006).

C. Extended Results

This extended results section will provide further details of the results of Study 1 in terms of the data screening, testing of assumptions, and the Bonferroni-Holm correction for multiple testing. The full findings of Studies 2 and 3 will also be provided.

3.1. Study 1: An Investigation into the Associations Between PPTs and Self-Reported Pain, Depression, Anxiety, and Demographic factors in knee OA

Response rate for questionnaire measures.

The response rate for the questionnaire pack (which included the BDI-II and STAI-SF) was 19%, which is low but in line with the response rates of other studies undertaken within the Arthritis Research UK Pain Centre.

Data screening.

The data for Study 1 were screened using recommendations by Tabachnick and Fidell (2013), details of which are provided below.

Inspection of univariate descriptives for accuracy of input.

Firstly, the raw data for all variables were checked for accuracy against the original record forms and any errors were rectified. Univariate descriptive statistics were also used to analyse the accuracy of the data input. No out-of-range values were found for any of the variables. For all participants, gender was recorded as ‘male’ or ‘female’, age ranged from 43 to 89 years (which is above the inclusion age of 18 years), and PPTs were all above zero (there is no upper limit for PPTs). See Table 12 for details of the range of values in the collected data and the possible ranges for the pain NRS, BDI-II, and STAI-SF totals.

Table 12.

Details of the actual and possible range of values for the BDI-II, STAI-SF and pain NRS factors.

Factor	Range of values in collected data	Possible range of data
BDI-II total	0 – 40	0 – 63
STAI-SF total	6 – 22	6 – 24
Pain NRS	2 – 10	1 – 10

Means, SDs, medians and inter-quartile ranges were reviewed for the variables, and these were assessed as plausible (i.e. no extreme values were found for these descriptive statistics). The presence of high SDs for the PPT data was in line with the findings of previous PPT QST research (Finan, Buenaver, et al., 2013) and was therefore not considered problematic.

The data was also screened for univariate outliers as part of inspecting the data for accuracy of input. For gender, no univariate outliers were detected as there was an approximately even split between the gender categories. For the continuous variables (age, pain NRS, BDI-II total, STAI-SF total, and the mean PPTs for the sternum, medial knee joint-line, lateral knee joint-line and medial tibia mid-shaft), univariate outliers were identified *via* the inspection of boxplots (see Appendix 12). This highlighted the presence of four univariate outliers for the mean sternum PPT, one for the mean medial knee joint-line PPT, three for the mean medial tibia mid-shaft PPT, and one for the BDI-II total. No univariate outliers were detected for age, mean lateral knee joint-line PPT, knee pain NRS, or STAI-SF total. Inspection of these univariate outliers confirmed that they were true outliers and were not inaccurately inputted into the dataset.

Missing data.

As data were missing for some of the factors, I checked whether this was missing at random (MAR). As MAR is not directly testable by statistical procedures

(Jaeger, 2006), I examined the data spreadsheet and the questionnaires and came to the conclusion that the data did not appear to be MAR (i.e. it appeared to be missing not at random, or MNAR). Data was missing for four participants for the mean medial knee joint-line PPT and for three participants for the mean lateral knee joint-line PPT. For these participants, PPT data was missing because it was not possible to reach the individuals' PPT for these body sites during the QST procedure (which suggests that their PPT was higher than for other participants at these sites). Data was also missing from 11 participants for the BDI-II total and from one participant for the STAI-SF total. For the participants with missing data from the BDI-II, eight participants were missing data from one questionnaire item only (item 1: one participant; item 4: one participant; item 21: six participants), two participants were missing data from two items (items 8 and 21: one participant; items 10 and 20: one participant), and one participant was missing data from 11 items (items 11 to 21). For the participant with a missing STAI-SF total score, this was because they did not respond to any items from the measure.

As the missing data appeared to be MNAR, I imputed the data using a maximum likelihood procedure (as this process can be unbiased with MNAR data despite the method assuming the data is MAR) (Schafer & Graham, 2002). In order to investigate the impact of the imputation, Spearman's correlations were calculated between the variables of interest for both the original data and the dataset which included the imputed values (as this analysis was planned as part of the first step of the multiple regression analyses). Inspection of these correlations showed no real differences, and so it appeared that the imputed data reflected statistical reality (Tabachnick & Fidell, 2013). Therefore, the subsequent aspects of the statistical analysis were conducted on the dataset with imputed values in place of the missing data. The STAI-SF missing data were not imputed as all items were missing for the one participant with missing STAI-SF data and so it was decided that it was more justifiable and meaningful to not impute this data. Therefore, all analyses including the STAI-SF total factor included data from 76 rather than 77 participants.

Testing the assumptions of multiple regression.

Linearity and homoscedasticity.

Linearity and homoscedasticity between all the continuous variables (the four PPT means; pain NRS; BDI-II total; and STAI-SF total) was assessed by examining bivariate scatterplots (see Appendix 13). These plots suggested that the relationships between variables were linear, but that many of the relationships were not homoscedastic (i.e. heteroscedastic: the variability in one variable appeared to not be the same at all values of another variable; Tabachnick & Fidell, 2013).

Normality.

Normality was assessed for the continuous predictor variables (pain NRS, BDI-II total and STAI-SF total) and for each of the outcome variables (mean PPT for the: sternum; medial knee joint-line; lateral knee joint-line; and medial tibia mid-shaft) by inspecting histograms and examining this statistically using the Kolmogorov-Smirnov test. All histograms for the variables suggested that they were not normally distributed (i.e. the distributions appeared skewed; see Appendix 14 for the histograms used for assessing the normality of these factors). This conclusion of non-normality was reinforced by the Kolmogorov-Smirnov test which was significant for all factors (at the $p < .05$ level) (sternum PPT mean: $D(77) = .131$, $p = .002$; medial knee joint-line PPT mean: $D(77) = .107$, $p = .030$; lateral knee joint-line PPT mean: $D(77) = .119$, $p = .008$; medial tibia mid-shaft PPT mean: $D(77) = .154$, $p < .001$; pain NRS: $D(77) = .120$, $p = .008$; BDI-II total: $D(77) = .144$, $p < .001$; STAI-SF total: $D(76) = .132$, $p = .002$).

Although the predictor variables (Pain NRS; BDI-II total; STAI-SF total) were not normally distributed, each had the minimum number of participants per predictor variable ($n = 15$; Field, 2009) and did not have bi-modal distributions, and so it was decided not to transform the data. This decision was based on guidance suggesting that predictors do not have to be normally distributed (Dancey & Reidy, 2011). However, outcome variables must be normally distributed (Dancey

& Reidy, 2011), and so the four mean PPT factors were transformed in order to meet this requirement. Log, square root and reciprocal transformations were calculated for each of the PPT outcome variables. Square root transformation resulted in the most normal distributions for the sternum, medial knee joint-line and lateral knee joint-line PPT means compared to the other transformation methods upon inspection of the histograms. For the medial tibia mid-shaft PPT mean, the log transformation appeared to result in a slightly more normal distribution than the square root transformation (as for the Kolmogorov-Smirnov test (log transformation): $D(77) = .064$, $p = .200$; whereas for the Kolmogorov-Smirnov test (square root transformation): $D(77) = .102$, $p = .047$). However, the histogram appeared normally-distributed for the square root transformation of the medial tibia mid-shaft PPT mean, and so this was assessed as leading to acceptable normality. Furthermore, although the four mean PPT factors were not be used in the same multiple regression models, it was judged as more consistent to use the same transformation method for all outcome variables.

Square root transformations of the PPT mean factors also appeared to retain linearity and improve the homoscedasticity for the variables of interest upon inspection of bivariate scatterplots (see Appendix 15). Therefore, the square root transformations of the outcome variables (rather than the non-transformed PPT means) were used for all subsequent analyses (i.e. for the remaining assumptions testing and for the correlation and multiple regression analyses. However, I will continue to refer to the PPT variables as '(body site) PPT mean' for conciseness.

Univariate outliers.

As briefly discussed previously as part of the data screening process, univariate outliers were assessed for each variable of interest (each PPT mean; gender; pain NRS; BDI-II total; and STAI-SF total) by inspecting boxplots for each factor (see Appendix 12). This analysis identified that the BDI-II factor had four univariate outliers (which represented participants with higher BDI-II totals than other participants), and the medial tibia mid-shaft PPT mean factor had one univariate outlier (which again represented a higher value than other

participants). No outliers for the other variables were found. In order to reduce the impact of the BDI-II total univariate outliers, this variable was transformed, as recommended by Tabachnick and Fidell (2013). The square root transformation procedure was used so as to use the same transformation method as for the PPT mean outcome variables (Field, 2009). This resulted in no univariate outliers for the transformed BDI-II variable, and this factor appeared to retain acceptable linearity and homoscedasticity (see Appendix 16). The square root transformed BDI-II total will be referred to as 'BDI-II total' for conciseness in the subsequent sections of the analysis. To deal with the impact of the univariate outlier for the medial tibia mid-shaft PPT mean, as the variable had already been transformed, it was decided to change the raw medial tibia mid-shaft PPT mean for this participant so that their score was still 'deviant' but not to the extreme that it was originally (based on recommendations by Tabachnick & Fidell, 2013).

Multivariate outliers.

Multivariate outliers were assessed for each planned outcome variable (i.e. the individual PPT means) along with the continuous predictor variables (pain NRS; BDI-II; STAI-SF). In the dataset, no cases had a Mahalanobis D^2 with a probability less than or equal to .001, and so it was concluded that no multivariate outliers were present in the dataset (Tabachnick & Fidell, 2013).

Multicollinearity.

Multicollinearity of the planned predictor variables pain NRS; BDI-II total; and STAI-SF total was assessed using Spearman's rho correlations (due to the NRS, BDI-II and STAI-SF providing ordinal level data; Field, 2009). Multicollinearity of the predictor variable gender was assessed using rank-biserial correlations due to its dichotomous nature and the ordinal level data of the other factors (the PPT data was reduced to ordinal level data due to the transformations undertaken: Osborne, 2002). None of the predictor values were found to correlate highly with each other (i.e. no r_s or r_{rb} value was over 0.9), and so the multiple regression assumption of no multicollinearity between predictors was upheld (Tabachnick & Fidell, 2013).

To calculate the rank-biserial correlations, the following formula was used: two times the difference between the mean ranks of the two groups (i.e. male and female gender) divided by the total sample size (Kraemer, 1982). See Appendix 17 for the SPSS output showing the mean ranks for men and women for each PPT, calculated using Mann-Whitney analysis. The calculations for the rank-biserial correlations between gender and each of the other study variables are shown in Table 13.

Table 13.

Calculations of rank-biserial correlations between gender and the other study factors.

Factor correlated with gender	**Calculation of r_{rb}**	**r_{rb}**	***P* of correlation ***
Sternum PPT	2((34.09-45.21)/77)	-.29	.030
Medial knee joint-line PPT	2((32.86-46.76)/77)	-.36	.007
Lateral knee joint-line PPT	2((33.79-45.59)/77)	-.31	.022
Medial tibia mid-shaft PPT	2((33.77-45.62)/77)	-.31	.021
Pain NRS	2((39.07-38.91)/77)	.00	.975
Depression	2((42.13-35.04)/77)	.18	.167
Anxiety	2((37.42-39.84)/77)	-.06	.633

**P*-values taken from Mann-Whitney analyses for each factor (see Appendix 17).

The remaining assumptions (normality of residuals and independent errors) were assessed following the multiple regression analysis as they required analysis of residuals.

Normality of residuals.

Inspection of residual normality P-P plots and of residuals scatterplots for each multiple regression model suggested that the normality of residuals assumption was met for all four regression analyses (i.e. the models with sternum, medial joint-line, lateral joint-line, and medial tibia mid-shaft as outcome variables) (see Appendix 18 for these plots regarding normality of residuals).

Autocorrelation.

The assumption of uncorrelated residuals (also known as lack of autocorrelation) for multiple regression analyses was tested with the Durbin-Watson test. The reference values provided by Durbin and Watson (1951) were used to compare the Durbin-Watson value for each final multiple regression model to in order to evaluate the autocorrelation assumption. The reference values used related to the probability value used in the analysis (p = .05), the sample size, and the number of predictors included in each analysis. Therefore, for each PPT regression model, the Durbin-Watson comparison values for four predictors were used. To investigate positive serial correlation, the Durbin-Watson statistic for each regression was compared directly to the reference values; and to assess negative serial correlation the reference values were compared against the value resulting from the calculation '4 minus the Durbin-Watson value' (Durbin & Watson, 1951).

There was no evidence of either positive or negative serial correlation for the any of the multiple regression models (sternum PPT: d = 1.78; medial knee joint-line PPT: d = 1.77; lateral knee joint-line PPT: d = 1.95; medial tibia mid-shaft PPT: d = 2.22). Therefore, none of the multiple regression models appeared to violate the autocorrelation assumption.

Bonferroni-Holm adjustment.

To correct for the repeated multiple regression testing (i.e. for each of the four PPT factors), the sequential Bonferroni-Holm adjustment was applied to the alpha

value for each regression model (Holm, 1979): see Table 14 for the corrected values.

Table 14.

Bonferroni-Holm corrected alpha values for each multiple regression model.

Multiple regression model *	**Bonferroni-Holm adjustment calculation**	**Corrected alpha value**
Medial tibia mid-shaft PPT	.05/4	.0125
Lateral knee joint-line PPT	.05/3	.0167
Medial knee joint-line PPT	.05/2	.025
Sternum PPT	.05/1	.05

* Sequence order of regression models was determined according to smallest to largest *p*-values, as per the Bonferroni-Holm method (Holm, 1979), for stage 2 of each regression model. *P*-values for the models were: medial tibia mid-shaft PPT = .001; lateral joint-line PPT = .003; medial joint-line PPT = .004; sternum PPT = .006.

The *p*-values for each multiple regression model (stage 2) were lower than the corrected alpha value for that particular model. Therefore, all models remained statistically significant following the application of the Bonferroni-Holm adjustment.

3.2. Study 2: An Investigation into the Inter-Rater Reliability of Pressure Algometry QST

Sample demographics.

The sample (*n* = 20) for Study 2 included 5 men (25% of sample) and 15 women (75% of sample). The age of participants ranged from 23 to 65 years, and the mean age was 42.00 years (*SD* = 12.01). Means of the PPT values at each body site were calculated for the participants (i.e. a mean of the PPT values for the body sites tested by researcher A and a mean of the data collected by researcher

B). Means of these PPT means were then calculated for each researcher so that there were four PPT means (for each body site) relating to the QST conducted by researcher A and four PPT means relating to the testing conducted by researcher B. Mean PPT data were available for all twenty participants for each body site, except for the medial knee joint line where only eighteen mean PPTs were included in the analysis. This is because medial knee joint line PPTs for two of the participants were not able to be recorded due to the testers being unable to apply enough pressure for the participants to indicate that their PPT level had been reached.

See Table 15 for the mean PPTs and *SD*s for each body site for both researchers separately. This shows that the PPTs collected by researcher B were consistently higher than those collected by researcher A for all body sites. The *SD*s, however, were of similar size, suggested similar variation in the PPT data collected by both testers.

Table 15.
Means and SDs of PPT data collected by each researcher.

	PPTs (kPa): mean (*SD*)	
Body site	**Researcher A**	**Researcher B**
Sternum	255.31 (149.56)	292.97 (154.48)
Medial knee joint-line	355.56 (191.86)	423.91 (190.60)
Lateral knee joint-line	416.34 (192.98)	473.59 (218.55)
Medial tibia mid-shaft	258.09 (165.03)	301.19 (170.10)

Inter-class coefficients.

ICCs (a measure of inter-rater reliability) were calculated for each QST body site to compare the PPT data collected by the two trained researchers. This provided quantification regarding the consistency of using the QST tool to measure PPTs

between the two testers. Qualitative descriptions of the ICC values were applied according to the system developed by Cicchetti (1994).

Sternum ICC.

For the sternum PPT data, the ICC was within the 'excellent' range (ICC = .803). The 95% CI for the sternum ICC ranged from the 'fair' to 'excellent' categories (95% CI [.562, .918]).

Medial knee joint-line ICC.

For the medial knee joint line PPT data, the ICC was within the 'excellent' range (ICC = .869). The 95% CI for the sternum ICC ranged from the 'fair' to 'excellent' categories (95% CI [.417, .960]).

Lateral knee joint-line ICC.

For the lateral knee joint line PPT data, the ICC was within the 'excellent' range (ICC = .828). The 95% CI for the sternum ICC ranged from the 'fair' to 'excellent' categories (95% CI [.581, .931]).

Medial tibia mid-shaft ICC.

For the medial tibia mid-shaft PPT data, the ICC was within the 'excellent' range (ICC = .869). The 95% CI for the medial tibia mid-shaft ICC ranged from the 'good' to excellent ranges (95% CI [.650, .949]).

3.3. Study 3: Rasch Analysis of the STAI-SF

Response rate.

The response rate for the questionnaire pack (which included the STAI-SF) was 19%, which is low but in line with the response rates of other studies undertaken within the Arthritis Research UK Pain Centre.

Demographics and questionnaire/NRS summaries.

The sample for Study 3 consisted of 143 (58.1%) females and 102 (41.5%) males, and participants ranged in age from 41 to 93. One participant did not disclose their gender or age. The median knee pain NRS rating for the sample (minus two cases of missing data) was 8, with an IQ range of 6 to 9. The median STAI-SF total score was 10, with an IQ range of 8 to 15. The total STAI-SF score was not possible to calculate for nine participants due to missing data, with five participants missing data for one STAI-SF item, one participant missing data for three items, and three participants missing data for all six STAI-SF items. See Table 16 for a summary of the participant characteristics for Study 3.

Table 16.

Summary of participant characteristics for Study 3.

	n	**%**
Gender		
Female	143	58.1
Male	102	41.5
Missing data for gender	1	0.4
	Mean	***SD***
Age (years)	68.04	9.46
	Median	**Inter-quartile range***
Knee pain NRS (range of possible scores: 1–10)	8	6 – 9
STAI-SF (range of possible scores: 6–24)	11	8 – 15

* 25th and 75th percentiles provided.

Rasch analysis.

Internal consistency of the STAI-SF data (prior to beginning the Rasch analysis) was found to be good (Cronbach's α=.874) (based on the criteria proposed by Kline, 1999).

For the initial Rasch analysis, five Class Intervals were used as this appeared to create the most equal group sizes, with the closest to 50 cases per group per STAIF-SF item, which is the recommendation (Psychometric Laboratory for Health Sciences, 2007). See Appendix 19 for the Class Interval distributions for a range of Class Interval numbers from two to six. The closest distributions to the recommendation of 50 cases per group per item were four and five Class Intervals. Five Class Intervals were selected as this resulted in a smaller range of Class Interval sizes (range: 27 to 47, a range of 20) than that of four Class Intervals (range: 36 to 63, a range of 27), which shows more equal Class Interval sizes of five groups of 'trait ability' (i.e. anxiety severity) were chosen.

All questionnaire items showed ordered thresholds, except for item 3 (*I feel upset*). Item 3 was therefore rescored by collapsing options 1 (*somewhat*) and 2 *(moderately*) into one response category. Therefore, instead of the possible response options being 0, 1, 2, or 3 (these are the adjusted values for the Rasch analysis), the response options for item 3 were changed to 0, 1, or 2 (coded 0112 in RUMM2020). This rescoring was selected as most appropriate because it resulted in the thresholds being ordered correctly and retained more scoring categories that other rescoring options, which is recommended (Psychometric Laboratory for Health Sciences, 2007). In the analysis in which item 3 was rescored, four Class Intervals were selected, as this resulted in groups of the most equal sizes closest to 50 per group per item (see Appendix 20).

See Table 17 for a summary of the initial Rasch analysis and the analysis with the scoring categories from item 3 rescored to 0112 ('item 3 rescored'). For both analyses, both item and person mean Fit Residuals were close to zero, and item and person *SD* Fit Residuals were approximately equal to the ideal value of 1, which suggests that both of these parameters show reasonable fit to the Rasch

model. The item-person interaction Chi-squared statistics for the initial analysis were non-significant (χ^2 (24) = 35.31, p >.05), which suggested fit between the STAI-SF data and the Rasch model for the Class Intervals. However, the item-person interaction Chi-squared statistics for the 'item 3 rescored' analysis were significant (χ^2 (18) = 30.87, p <.03), which suggested misfit to the Rasch model for the Class Intervals. The mean location of persons was -1.17 in the initial Rasch analysis and -1.25 in the rescore item 3 analysis, which are both lower than the centralised mean of the items (zero). This shows that, in general, the participants in the sample reported lower anxiety than the average 'difficulty' level the STAI-SF (i.e. the level of anxiety it is designed to measure).

Both the 'initial analysis' and 'item 3 rescored' scales passed the test of unidimensionality. Principal Components Analyses identified three items which loaded positively onto the first component (items 1, 4, and 5), and three items which loaded negatively onto the first component (items 2, 3, and 6) (these item groupings were the same for both analyses). For the initial Rasch analysis, 12 out of 208 *t*-tests (5.77%; Binomial CI: 2.80-8.70%) comparing these two groups of items were significant. For the 'item 3 rescored analysis', 11 out of 208 *t*-tests (5.29%; Binomial CI: 2.30-8.30%) were significant. Although the percentage of significant *t*-tests was over 5% for both analyses, the lower 95% CI limits for both analyses was below 5%, and so unidimensionality could be assumed.

Table 17.

Summary of the fit statistics for the initial and 'item 3 rescored' analyses of the STAI-SF.

Rasch analysis	Number of STAI-SF items included	Item fit residual (mean)	Item fit residual (*SD*)	Person fit residual (mean)	Person fit residual (*SD*)	Chi-squared (*df*)	*P*-value	PSI	% of significant *t*-tests (proportion CI)
Initial	6	0.26	1.19	-0.39	1.09	35.31 (24)	.06	.87	5.77% (2.80-8.70%)
Item 3 rescored	6	0.32	1.32	-0.37	1.09	30.87 (18)	.03	.86	5.29% (2.30-8.30%)
Ideal values	*Not applicable (N/A)*	*0.00*	*1.00*	*0.00*	*1.00*	*N/A*	*>.05*	*>.70*	*<5% (Lower CI value <5%)*

As rescoring item 3 did not improve the fit of the data, and in fact resulted in a worse fit (i.e. the item-person interaction Chi-squared statistic became significant), the original scoring was retained. Therefore, the subsequent results are based on the initial analysis.

There was no evidence of response dependency (i.e. no positive correlations above r = .30 were evident between any of the item residuals). Indeed, the correlations between the item residuals ranged from r = -.46 to r = .18. Similarly, no DIF was evident for age or gender (i.e. no significant main or interaction effects were found for any item in the two-way factorial ANOVA tests with Bonferroni adjustment, i.e. significance set at $p < .01$). In the ANOVA tests concerning age group, there were no significant main effects (assessing uniform DIF) of age group on the responses for any of the six STAI-SF items (item 1: F (2, 191) = 0.65, $p > .05$; item 2: F (2, 191) = 0.70, $p > .05$; item 3 F (2, 190) = 0.62, $p > .05$; item 4: F (2, 191) = 0.64, $p > .05$; item 5: F (2, 192) = 0.12, $p > .05$; item 6: F (2, 192) = 0.50, $p > .05$). There were also no significant interaction effects (assessing non-uniform DIF) between age group and Class Interval on the responses for any of the STAI-SF items (item 1: F (8, 191) = 1.43, $p > .05$; item 2: F (8, 191) = 1.48, $p > .05$; item 3: F (8, 190) = 1.70, $p > .05$; item 4: F (8, 191) = 1.07, $p > .05$; item 5: F (8, 192) = 0.44, $p > .05$; item 6: F (8, 191) = 1.02, $p > .05$). In the ANOVA tests concerning gender, there were no significant main effects of gender on the responses for any of the STAI-SF items (item 1: F (1, 196) = 3.89, $p > .04$; item 2: F (1, 196) = 0.0001, $p > .05$; item 3: F (1, 195) = 1.02, $p > .05$; item 4: F (1, 196) = 4.01, $p > .04$; item 5: F (1, 197) = 3.44, $p > .05$; item 6: F (1, 197) = 0.63, $p > .05$). There were also no significant interaction effects between gender and Class Interval on the responses for any of the STAI-SF items (item 1: F (4, 196) = 1.45, $p > .05$; item 2: F (4, 196) = 2.08, $p > .05$; item 3: F (4, 195) = 0.77, $p > .05$; item 4: F (4, 196) = 0.28, $p > .05$; item 5: F (4, 197) = 1.17, $p > .05$; item 6: F (4, 197) = 1.78, $p > .05$).

To investigate individual person fit the fit residuals for each participant were examined. Six individuals (2.44% of the sample) responded in an unexpected way (according to the Rasch model) in that they showed misfit (i.e. their fit residuals were outside of the fit residual range of -2.5 to 2.5). All of these six

misfitting individuals had high negative fit residuals (i.e. below -2.5), which suggests that their responses were too deterministic (Moreton et al., 2012). There appeared to be no gender bias in these misfitting individuals (female % = 50%). However, there was evidence for some bias in terms of age group (under 65 years = 16.67%; 65 to 71 years = 66.67%; 72 years and over = 16.67%). These six individuals were removed from the analysis. In line with guidelines from Linacre (2010) to establish whether it is beneficial to remove individuals from the analysis, I cross-plot the person estimates (i.e. the person locations) from the initial analysis against those from the analysis with six people deleted. As there were several changes to person locations (notable from the non-linear configuration of some of the data points on the cross-plot: see Figure 2), it was decided to leave the six individuals deleted from the analysis.

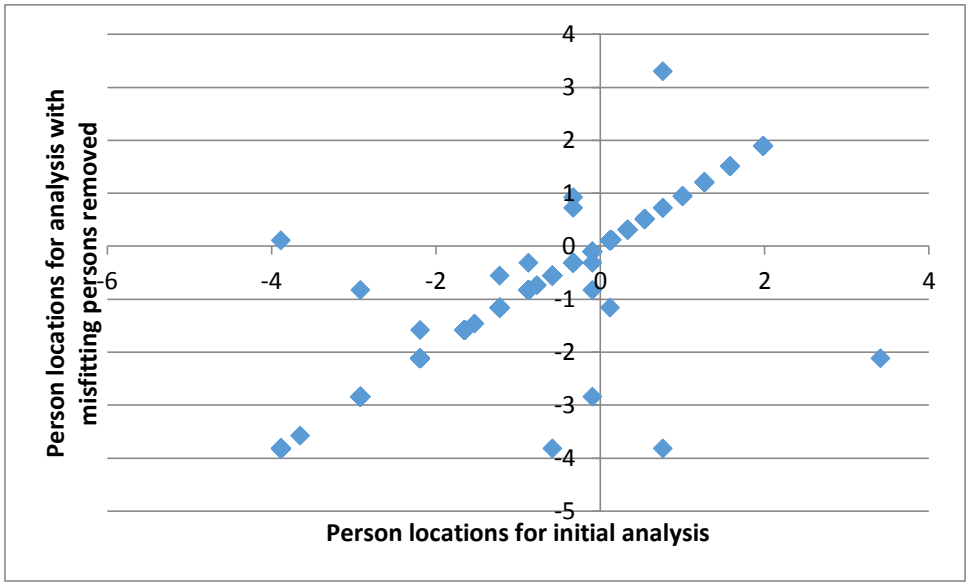

Figure 2. Plot of person locations for the initial analysis and for the analysis with misfitting participants removed.

Once the six misfitting persons were removed, the analysis included two individuals with high negative fit residuals (who did not have high fit residuals in the initial analysis). However, their removal did not result in significant changes in person locations, when the person locations from the 'six persons removed' analysis were cross-plot against the person locations from the 'eight people removed' analysis (see Figure 3). Therefore, the 'six people removed' analysis

was used and the two further individuals considered for removal were retained in the analysis.

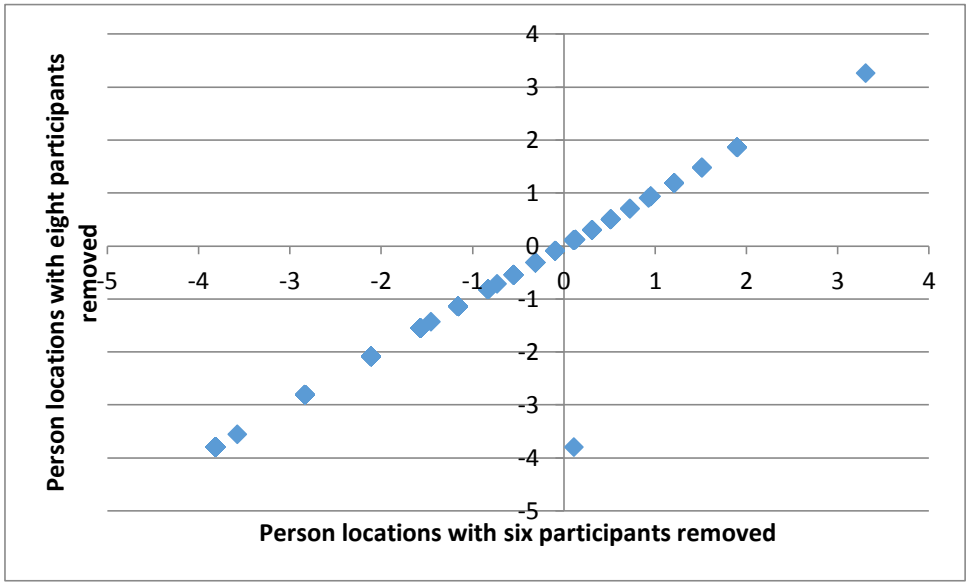

Figure 3. Plot of person locations for the analyses when six and eight misfitting participants, respectively, were removed.

However, as shown in Table 18, the deletion of the six misfitting individuals in the initial analysis resulted in a worsened item-person interaction Chi-squared statistic, which was significant (χ^2 (18) = 30.93, p <.03), which suggested misfit to the Rasch model for the Class Intervals. As the initial analysis (with no removed persons) resulted in the best fit statistics, all individuals were included in the analysis.

Table 18.

Summary of the fit statistics for the initial and 'six persons removed' analyses of the STAI-SF.

Rasch analysis	Number of STAI-SF items included	Item fit residual (mean)	Item fit residual (*SD*)	Person fit residual (mean)	Person fit residual (*SD*)	Chi-squared (*df*)	*P*-value	PSI	% of significant *t*-tests (proportion CI)
Initial	6	0.26	1.19	-0.39	1.09	35.31 (24)	.06	.87	5.77% (2.80-8.70%)
Six persons removed	6	0.16	1.16	-0.35	0.98	30.93 (18)	.03	.86	5.94% (2.90-8.90%)
Ideal values	*Not applicable (N/A)*	*0.00*	*1.00*	*0.00*	*1.00*	*N/A*	*> .05*	*> .70*	*< 5% (Lower CI value < 5%)*

In the initial Rasch analysis, extreme scores (i.e. the minimum or maximum possible scores on the STAI-SF) were found for 35 participants (14.77% of 237 participants who completed all STAI-SF items). The lowest possible STAI-SF total was scored by 34 participants (14.35% of 237 participants who completed all STAI-SF items), and the highest possible STAI-SF total was scored by one participant (0.42% of 237 participants who completed all STAI-SF items). Therefore, based on the recommendation to conclude the presence of floor or ceiling effects if over 15% of a sample score extreme scores (Terwee et al., 2007), it was concluded that floor/ceiling effects were not present in the STAI-SF of the sample in the current study.

In the initial analysis, no items demonstrated misfit to the Rasch model (i.e. no items had high fit residuals above 2.5 or below -2.5, had significant Chi-squared statistics, or had significant ANOVA statistics following a Bonferroni adjustment). For the six items in the initial analysis, the fit residuals ranged from -1.85 to 1.66. The Chi-squared analyses found no significant differences between observed or expected scores for any of the STAI-SF items (item 1: χ^2 (4) = 6.31, $p > .05$; item 2: χ^2 (4) = 5.08, $p > .05$; item 3: χ^2 (4) = 3.76, $p > .05$; item 4: χ^2 (4) = 7.10, $p > .05$; item 5: χ^2 (4) = 4.04, $p > .05$; item 6: χ^2 (4) = 9.01, $p > .05$). The ANOVA tests (with Bonferroni correction, i.e. significance set at $p < .01$) showed no significant differences between observed and estimated item scores across the Class Intervals (item 1: F (4, 202) = 1.81, $p > .05$; item 2: F (4, 202) = 1.11, $p > .05$; item 3 F (4, 201) = 0.79, $p > .05$; item 4: F (4, 202) = 3.09, $p > .01$; item 5: F (4, 203) = 1.07, $p > .05$; item 6: F (4, 203) = 0.50, $p > .03$).

To more fully assess the impact of removing the misfitting persons (the ‘six persons removed’ analysis), individual item fit was also investigated for this analysis. Items 1, 2, 3, 5 and 6 did not show misfit (i.e. no items had high fit residuals above 2.5 or below -2.5, had significant Chi-squared statistics, or had significant ANOVA statistics following a Bonferroni adjustment). For these five items, the fit residuals ranged from -1.90 to 1.51. The Chi-squared analyses found no significant differences between observed or expected scores for these five STAI-SF items (item 1: χ^2 (3) = 7.42, $p > .05$; item 2: χ^2 (3) = 2.81, $p > .05$; item

3: χ^2 (3) = 5.19, p > .05; item 5: χ^2 (3) = 1.18, p > .05; item 6: χ^2 (3) = 7.27, p > .05). The ANOVA tests (with Bonferroni correction, i.e. significance set at p < .01) for these five questionnaire items showed no significant differences between observed and estimated item scores across the Class Intervals (item 1: F (3, 197) = 2.91, p > .03; item 2: F (3, 197) = 0.71, p > .05; item 3 F (3, 196) = 1.55, p > .05; item 5: F (3, 198) = 0.51, p > .05; item 6: F (3, 198) = 0.50, p > .04). However, in the 'six persons removed' analysis, item 4 did demonstrate misfit to the model, as the ANOVA test (with Bonferroni correction, i.e. significance set at p < .01) for this item showed a significant difference between observed and estimated item scores across the Class Intervals: F (3, 197) = 4.18, p < .01. This provides further evidence that removing the misfitting persons has a detrimental impact on other important aspects of the data fit and suggests that the initial analysis model provides the best fit to the Rasch model.

As the initial analysis model (i.e. with no items rescored and no items/persons removed) was shown to be the most appropriate fit to the Rasch model, this analysis was used as the 'final scale'. The person-item threshold distribution of the initial analysis was inspected (see Figure 4). The distribution suggests that the scale was not well targeted, as the person locations (i.e. score on the STAI-SF) are not normally distributed across the item thresholds.

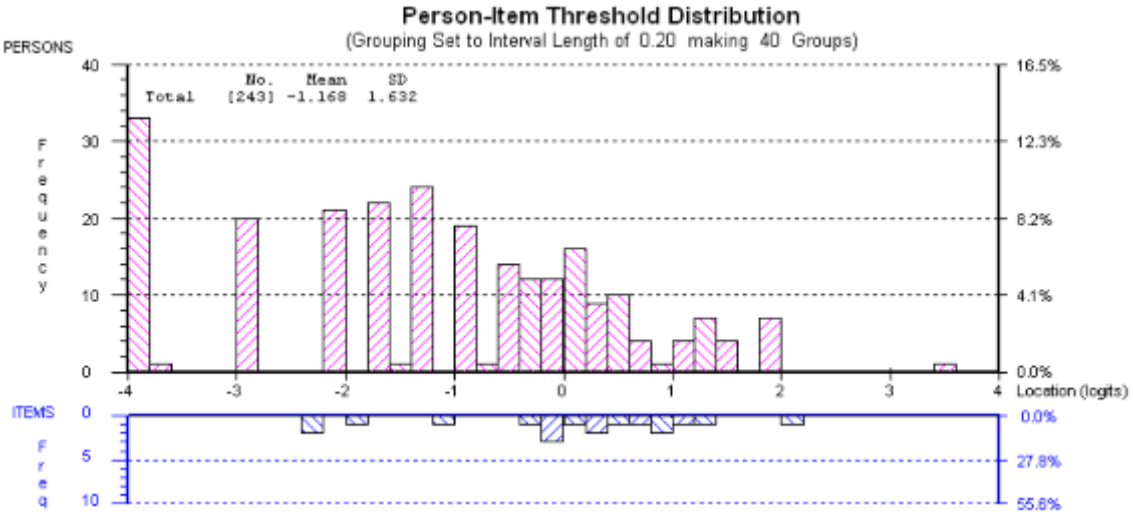

Figure 4. Person-item threshold distribution for the initial Rasch analysis of the STAI-SF.

As the initial analysis showed fit to the Rasch model, it was possible to provide 'Rasch values' (i.e. person locations) to convert raw STAI-SF scores for each item into interval level data (Tennant & Conaghan, 2007). See Table 19 for the conversion values. The 'Rasch values' were also transformed into scaled scores, based on guidance in Psychometric Laboratory for Health Sciences (2007) and Raw score-to-measure (2007).

The following formula was used to transform the logit Rasch values into scaled scores (where *y* is the scaled score, *s* is the wanted range divided by the current range, and *m* is the wanted minimum score divided by the value when the current minimum score is multiplied by *s*):

***y* = *m* + (*s* multiplied by person location)** (Raw score-to-measure, 2007).

In this case, *s* = 2.466 and *m* = 15.59.

Table 19.

Rasch conversion scores and scaled scores for the STAI-SF.

Raw STAI-SF total score	**Rasch value**	**Standard Error**	**Scaled score**
6	-3.89	1.30	6.00
7	-2.92	0.98	8.39
8	-2.20	0.79	10.16
9	-1.65	0.69	11.52
10	-1.22	0.62	12.58
11	-0.88	0.57	13.42
12	-0.59	0.53	14.14
13	-0.33	0.50	14.78
14	-0.10	0.49	15.34
15	0.12	0.48	15.89
16	0.33	0.48	16.40
17	0.54	0.48	16.92
18	0.76	0.49	17.46
19	1.00	0.52	18.06
20	1.27	0.55	18.72
21	1.58	0.61	19.49
22	1.98	0.70	20.47
23	*Values not available as there was no corresponding person location in the analysis*		
24	3.41	1.27	24.00

D. Extended Discussion

This extended methods section will include a discussion about the thesis research as a whole. I will then go on to highlight potential areas of limitation for Studies 1, 2, and 3 separately. I will discuss implications of the research, before providing a critical reflection regarding this research.

The main aim of this thesis research was to investigate the relationships between PPTs, reported pain, depression, and anxiety for people with knee OA. The results of Study 1 suggest that there may be a small relationship between mood and PPTs in knee OA, with higher levels of depression and anxiety in the presence of lower PPTs. This is in line with previous knee OA research (e.g. Finan, Buenaver, et al., 2013), and may indicate that higher levels of depression and anxiety are associated with higher central sensitisaion if one accepts the suggestion that QST measures this central pain process. The current study also replicates the common finding of higher pain thresholds in men compared to women (e.g. Riley III et al., 1998). However, interestingly, Study 1 did not find any evidence of a correlation between gender and pain NRS. Putting these results together could suggest that there is either evidence for a real gender difference in central sensitisation but not pain intensity in knee OA. However, it could also suggest that there was something about the QST procedure which produced this gender difference, such as the influence of gender role socialisation (i.e. male participants not wishing to show 'weakness' by 'admitting' that their PPT had been reached; Wise, Price, Myers, Heft, & Robinson, 2002) or the influence of the researchers' characteristics (who were both female; Kállai, Barke, & Voss, 2004).

Although demand characteristics and experimenter effects in QST studies with healthy participants have received some attention in the literature (e.g. Kállai et al., 2004), this is not the case for QST studies with clinical groups, such as individuals with knee OA. Indeed, in the literature, QST is considered an objective measure of pain sensitivity in musculoskeletal disorders (Courtney et al., 2010). This thesis research suggests that there can be an acceptable level of inter-rater reliability in PPT QST (as found in Study 2), but much more investigation of the impact of contextual and social factors on PPTs and other QST data is needed.

This is crucial in order to be able to fully understand and interpret research findings regarding any associations between QST data and other factors. Furthermore, it is important that these potential contextual issues regarding the use of QST are understood before QST is introduced as an assessment tool or outcome measure within in clinical practice with patients with knee OA and other painful conditions, as has been advocated within the literature (Pavlaković & Petzke, 2010).

This research project also highlighted potential measurement issues in using the STAI-SF with knee OA patients. The Rasch analysis conducted in Study 3 found that the STAI-SF was mistargetted, in that it did not measure the low levels of anxiety expressed by a substantial proportion of the knee OA sample. Furthermore, the low mean person location in the Rasch analysis summary statistics for the final analysis model also suggested that many of the participants had a low level of anxiety as measured on the STAI-SF. This suggests that a measure of anxiety to be used with people with knee OA could benefit from having more items measuring lower 'difficulty' (i.e. lower levels of anxiety). It may be that the DAPOS measure (Pincus, Williams, Vogel, & Field, 2004) is a more appropriate measure of mood in this client group, although there appear to currently be no published Rasch analyses of the DAPOS in a knee OA sample or any other chronic pain group to comment on the targeting of this measure compared to the STAI-SF.

In summary, the minimal influence of mood found on PPTs found in Study 1 could have been influenced by measurement issues with the STAI-SF and pressure QST methodology. This suggests that it is important for researchers to identify and attempt to rectify concerns with these pain/mood assessment tools so that findings in knee OA research studies using these tools are more robust. Furthermore, the robustness of assessment tools of pain and mood in clinical practice is also extremely important so that the assessment findings are as reliable as possible.

In terms of how these research findings (particularly from Study 1) add to the psychological models of pain and mood, it is not possible to ascertain causation

and directionality of the (small) relationships found between depression/anxiety and PPTs due to the correlational design of Study 1. However, if PPTs are a quantification of central sensitisation (which could be contested, as previously discussed), then it could be placed within existing psychological models of pain based on existing theoretical understandings. All of the psychological models discussed in the background to this thesis propose that depression and anxiety in response to an initial pain experience can maintain the experience of pain and lead to a chronic pain process, *via* different psychological processes (such as fear-avoidance, cognitive enmeshment, and lack of acceptance). Therefore, as central sensitisation is thought to be caused by repeated nociception (Courtney et al., 2010), then it makes theoretical sense that if depression and anxiety can lead to further pain (i.e. repeated nociception), then central sensitisation could eventually develop.

It would be beneficial to conduct further QST research using a range of measures of the psychological factors that are key to the main psychological models discussed in the background section (fear-avoidance, diathesis-stress, enmeshment, and acceptance models) in order to develop these models to include a consideration of central sensitisation.

Study 1, however, does suggest that it may be important that psychological models of the pain-mood relationship also include more social factors, such as gender role expectations. This conclusion is novel within the knee OA literature base. Although existing psychological models of chronic pain do provide some space to consider social factors, they are all fairly individualistic and do not position wider systemic influences as central to the pain experience. This reflects the dominance of cognitive-behavioural theory and intervention in the chronic pain field (Roy, 2008), but does mean that wider social discourses and contextual factors may be overlooked in the assessment and management of pain, depression, and anxiety for people with knee OA and other chronic pain conditions.

Limitations of the Separate Sub-Studies

4.1. Study 1: An investigation into the associations between PPTs and self-reported pain, depression, anxiety, and demographic factors in knee OA.

It is important to acknowledge the potential limitations of Study 1. It has already been suggested that other psychological factors (such as catastrophising, fear-avoidance, and pain acceptance) may be more associated with central sensitisation than depression and anxiety were found to be. It may have also been beneficial to include positive affect in the regression models, as this protective factor is beginning to be considered as important in both the general chronic pain literature (e.g. Pincus et al., 2004) and the QST OA literature (e.g. Finan, Quartana, & Smith, 2013). However, it was beyond the remit of this thesis research to recruit a large enough sample to include all of these variables as predictors in the multiple regression models. Also, the mood factors that were included in Study 1 (depression and anxiety) are the dominant psychological factors within the literature base, and so it was judged as important to include these variables above other potentially relevant factors.

In terms of the accuracy and generalisability of the multiple regression analyses, although the data which violated the assumptions was transformed or adjusted, this does mean that for some of the factors included in the analyses, the data were not the actual responses from participants, which some authors believe is problematic (Field, 2009). Furthermore, although the sample size met the requirements for the 'rule of thumb' of 15 participants for each predictor factor (Field, 2009), it did not meet the more conservative sample size calculated of 85 participants, which could jeopardise the accuracy and validity of the multiple regression findings. Also, although the adjusted *R* squared was used in the multiple regression models so as to better reflect the real-world population (Dancey & Reidy, 2011; Tabachnick & Fidell, 2013), Field (2009) has queried the ability of this adjustment to improve model generalisability.

Finally, as the participants for Study 1 were recruited from the participants who completed the questionnaire pack (within the wider pain centre project), there may be issues regarding response bias and whether the sample in Study 1 are representative of all people with knee OA. As this study required participants to attend a University of Nottingham research location, it may be that this excluded potential participants who were not able to travel, for example due to severe physical disability or psychological difficulties. This highlights the importance of considering the study's findings within these limits on generalisability.

4.2. Study 2: An investigation in the inter-rate reliability of pressure algometry QST.

The finding of acceptable inter-rater reliability between the two QST administrators should be interpreted within the context of a number of potential limitations. As the sample in Study 2 included healthy participants with a younger mean age than the knee OA sample in Study 1, the representativeness of the inter-rater reliability findings could be questioned. However, it has been suggested that inter-rater reliability of QST is not affected by pain status or demographic characteristics (Chesterton et al., 2007), and so this may not be a substantial limitation. Furthermore, Study 2 was designed to assess the inter-rater reliability of the pain-pressure QST at four specific body sites (sternum, medial knee joint-line, lateral knee joint-line, and medial tibia mid-shaft) between the two researchers who administered the QST in this thesis research. Therefore, the findings of acceptable inter-rater reliability are not generalisable to other QST methodology, other personnel administering the QST, or other body sites.

4.3 Study 3: Rasch analysis of the STAI-SF.

In terms of potential limitations specifically of the Rasch analysis sub-study (Study 3), the fairly low questionnaire response rate may suggest the presence of response bias, which could limit the generalisability of the Rasch findings. Furthermore, a Rasch solution of the STAI-SF data without mistargetting was not found, which could suggest a lack of external validity of the questionnaire with knee OA patients (which obviously has implications for the interpretation of the

findings of Study 1). Also, the high proportion of negative fit residuals in the analysis of person fit shows that a substantial proportion of the responses were too *deterministic*, which means that participants consistently scored the same value for each item (Moreton et al., 2012) (in this case: the lowest score for all items). This is a problem in Rasch analysis, and could have lowered the accuracy and generalisability of the findings. However, determinism is more likely when a measure has a small number of questions, as in the case of the STAI-SF, and short measures of mood are often considered more appropriate in research with large questionnaire packs (as in the case of the wider study this thesis research sits within) and in clinical practice.

Summary of Discussion and Implications

This study provides evidence for questioning the appropriateness of conceptualising QST as an 'objective' measure of pain/'central sensitisation' in knee OA, and suggests that further research is required to investigate contextual factors involved in the QST process which could impact the data it provides. This is particularly important if QST is used in clinical practice to select subgroups of patients who could benefit from additional interventions such as psychological therapy (as has been suggested in the literature). If QST was used is this way within clinical practice, then it would clearly have a direct impact on the work of Clinical Psychologists within chronic pain settings. Therefore, it is important that Clinical Psychologists remain involved in QST research so that they are able to apply a psychological understanding to findings prior to the potential introduction of the methodology into the clinical settings they may work within.

Critical Reflection

I will now provide a critical reflection on the research included in this thesis, with a focus on the research process and the theoretical, scientific and ethical contexts.

Research process.

I believe that conducting this study within a multi-disciplinary research centre has impacted on the research process. There have been many positives to this, such as having access to methodology I would not have had otherwise (i.e. QST), and being able to network with a large group of researchers with expertise in knee OA and chronic pain. However, conducting the research within the research centre has created a challenge in terms of the control I have over the studies. I managed this challenge by ensuring I had input into the research, which I did by selecting the factors I would focus on in Study 1, and by shaping the research by suggesting the addition of the inter-rater reliability study. From discussions with research colleagues based in large research centres, I have come to appreciate that this challenge of having individual control over research is often part of the nature of larger scale research. It is likely that part of this pressure I felt to have 'enough control' over the study was linked to that fact that my research work is part of my training and my contribution will be assessed. Furthermore, I was 'warned' by several tutors on my training courses to ensure that I had adequate input into the research, which no doubt impacted on my feelings around this aspect of the research process.

Finally, although all three sub-studies included in this thesis are linked to the main research question (in Study 1), the multi-study nature of the thesis has, during the process, challenged me in terms of attempting to produce a coherent thesis and a coherent piece of research. Research supervision has helped me to develop my thinking around the 'unifying thread' in my research. Also, reading publications regarding other quantitative research of doctoral-level (or above) has enabled me to appreciate that most quantitative studies have secondary aims and sub-studies within them. Throughout the research process, it has felt important to ask myself the question 'why am I doing this and how does it relate to my main research question?'.

Theoretical context.

This research has positivist epistemological underpinnings, with an aim to find an 'objective truth'. However, throughout my training alongside the completion of this thesis, I have learned more about qualitative research methods, and critical realist and social constructionist epistemologies. I think this may have impacted on how I have approached aspects of the research, which is likely to be different (and potentially more critical) than medical research colleagues within the research centre. For example, during the data collection, I have wondered myself what 'pain' means to people, and what their experiences of pain and expressing pain have been like and how they have impacted on them, if at all. Remaining faithful to the positivist theoretical context has also been challenged during the data collection process when participants have shared their experiences of how knee OA has affected them, and I felt interested in these stories. The questionnaires used aimed to capture some of this, but I felt, at times, that the reductionism of my quantitative approach may not have fully captured participants' experiences.

Related to my experiences of the limitations of a quantitative approach, I have been able to reflect on the differences between my position in regards to the theoretical underpinnings of the research and that of other researchers involved in the wider research project. For example, the gender difference in PPTs found in Study 1 has been interpreted by some colleagues in the research centre as 'full-proof' evidence for an innate difference in pain perception between males and females. I am reluctant to accept this explanation, and, although I do see a role for biological mechanisms in the experience of pain, I think that the gender differences found in this research must be considered in the light of the impact that the QST testers' ages and gender may have had, as well as the impact of gender role expectations. The different way I have considered these results compared to other (more medical) researchers has helped me appreciate the benefits of having a multidisciplinary research team in order to conduct pain research based on rich understandings of many of the different factors involved in the experience and expression of pain. My experiences of conducting this research in a fairly medical research environment has also helped me consider the dominant discourses regarding knee OA that clients are privy too, and how

taking part in psychological research may seem very ‘different’ to most of the clinical and research contexts a person with knee OA would usually experience.

Scientific context.

Through conducting psychological research focussed on a physical health condition, I have often felt a ‘pull’ to justify this research, potentially to a greater extent than I would have done if my research was focussed on a mental health difficulty. I have wondered whether the requirements of my training course has impacted on this, which state that enough psychological theory must be included. I also think that the dominance of medical research in the field of knee OA has affected my experience of the scientific context, and I have felt equally ‘pulled’ to communicate the importance of a psychological understanding in pain conditions such as knee OA to medical research colleagues involved in the wider research project. My position as a psychological researcher in a medical area has also highlighted the tensions between medical and psychological views of ‘science’, and I appreciate that this is a challenging position to hold, but one with potential to develop very novel understandings in a traditionally medical domain.

The use of statistics in this research has also led me to reflect on the dominance of the common discourse around statistics within quantitative research as being an objective science. There have been many stages during the statistical analyses where I have had to make decisions and judgements which then affected the final results. Although I aimed to make the best judgements based on the data and appropriate guidelines, this process has helped me to appreciate the importance of having clear justifications for the choices made in statistical analyses and to be more critically aware of the decisions made in the analyses within other research, rather than taking the results at ‘face value’. This critical awareness of the nature of statistics in scientific research is also likely to benefit future research I conduct.

Ethical context.

As this thesis research is part of a much wider project in a large research centre, the ethical approvals for Studies 1 and 3 were already in place when I became involved. I have learned a lot from research supervision regarding the complexity of gaining ethical approval from multiple NHS trusts for research which is frequently evolving and requiring ethical amendments. I was pleased to have more direct involvement in the ethics application for Study 2, and want to ensure that I gain more experience of producing ethics applications in my future research career.

Finally, the wider research project that this thesis sits within has produced very large data sets with data from a wide number of questionnaires. I have reflected on the ethical implications of this, and although it was beyond the remit of my research questions and this thesis to analyse all of the data, it is very important that all of the data is used in future publications by the research centre. It seems necessary, on an ethical level, to value all of the information collected from participants, and I believe it is important to remember this in the case of large data sets, where it could be easy to just think of the data as data, rather than as personal information volunteered by people experiencing a painful medical condition. This is a belief that I will carry with me into my future research career, particularly if I am involved in studies with large data sets.

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Appendices

Appendix 1.

Search strategy

The following limits were placed on the search strategy: clinical trial or randomized controlled trial or controlled clinical trial or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial; humans; adults; English language studies; peer-reviewed journal; remove duplicates.

Osteoarthritis

1. osteoarthritis/
2. osteoarthritis/
3. osteoarthritis, hip/
4. osteoarthritis, spine/
5. osteoarthritis, knee/
6. osteoarthrosis/
7. gonarthritis/
8. gonarthrosis/
9. gonitis/
10. coxarthritis/
11. coxarthrosis/
12. coxitis/
13. (osteophyte$).mp.
14. (joint space adj6 narrow$).tw.
15. (degenerative adj2 arthritis or osteoarthr$ or osteo-arthritis).mp.
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

Psychological intervention

17. CBT/
18. (cognitive behav$ therap$).mp.
19. cognitive behav$ treatment/
20. cognitive behav$ intervention/
21. (cognitive therap$).mp.
22. cognitive treatment/

23. cognitive intervention/
24. (behav$ therap$).mp.
25. behav$ treatment/
26. behav$ intervention/
27. computerised CBT/
28. (computerised cognitive behav$ therap$).mp.
29. computerised cognitive behav$ treatment/
30. computerised cognitive behav$ intervention/
31. CCBT/
32. cCBT/
33. ACT/
34. (acceptance and commitment therap$).mp.
35. (acceptance commitment therap$).mp.
36. (acceptance and commitment).mp.
37. acceptance-based/
38. (acceptance based).mp.
39. mindfulness/
40. meditation/
41. vipassana/
42. mindfulness based stress reduction/
43. mindfulness-based stress reduction/
44. MBSR/
45. (mindfulness based cognitive therap$).mp.
46. (mindfulness-based cognitive therap$).mp.
47. MBCT/
48. relaxation/
49. (family therap$).mp.
50. (systemic therap$).mp.
51. (couple therap$).mp.
52. (couples therap$).mp.
53. pain management group/
54. PMG/
55. Pain management programme/
56. Pain management program/

57. PMP/
58. pain management training/
59. self-management group/
60. self-management training/
61. self management group/
62. self management training/
63. educational intervention/
64. psychoeducation/
65. psychoeducational/
66. psychoeducational intervention/
67. psychoeducational treatment/
68. (psychoeducational therap$).mp.
69. psychosocial intervention/
70. psychosocial treatment/
71. (psychosocial therap$).mp.
72. psychological education/
73. psychological intervention/
74. psychology intervention/
75. (psychological therap$).mp.
76. (psychology therap$).mp.
77. (psychotherap$).mp.
78. counselling/
79. counseling/
80. hypnotherap$.mp.
81. guided imagery/
82. arthritis self-management/
83. arthritis self management/
84. self-management/
85. self-care/
86. self-help/
87. self-improvement/
88. self management/
89. self care/
90. self help/

91. self improvement/
92. patient education/
93. patient teaching/
94. patient training/
95. expert patient/
96. (non surgical or non-surgical or non pharmacological or non-pharmacological or conservative management or conservative therap$).mp.
97. (group program or group programme or group therap$).mp.
98. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97

Anxiety

99. anxiety/
100. GAD/
101. generalised anxiety disorder/
102. generalised anxiety/
103. generalized anxiety disorder/
104. generalized anxiety/
105. panic disorder/
106. panic/
107. agoraphobia/
108. agoraphobic/
109. health anxiety/
110. health phobia/
111. health-related anxiety/
112. health related anxiety/
113. social anxiety/

114. social phobia/
115. PTSD/
116. post-traumatic stress disorder/
117. posttraumatic stress disorder/
118. post-traumatic stress/
119. posttraumatic stress/
120. OCD/
121. obsessive compulsive disorder/
122. obsessive-compulsive disorder/
123. phobia/
124. phobic/
125. fear/
126. state anxiety/
127. trait anxiety/
128. anxious/
129. stress psychological/
130. (anxi$ or agitat$ or nervous$ or apprehen$ or worr$ or stress$).mp.
131. 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130

Full Search: 16 and 98 and 131

Appendix 2

Letter of access for my involvement in the research and an email regarding the approval needed for my involvement

Nottingham University Hospitals NHS
NHS Trust

Research & Innovation
Nottingham Integrated Clinical Research Centre
C Floor, South Block
QMC Campus
Derby Road
Nottingham
NG7 2UH

Tel: 0115 970 9049

www.nuhrise.org

RSCH 282a

29/04/2013

Ms Victoria Tew
3 Scott Court
Scott Street
Leicester
LE2 6EZ

Dear Victoria

Re: Letter of Access for Research

Study Title:	Measures of pain relevant to knee osteoarthritis	
Chief Investigator	Bryan Moreton	
Local Collaborator at NUH:	Prof. Nadina Lincoln	
R&D Ref:	10RH008	CLRN ID 57488
Sponsor:	Univ of Nottingham	

As an existing NHS employee you do not require an additional honorary research contract with this NHS organisation. We are satisfied that the research activities that you will undertake in this NHS organisation are commensurate with the activities you undertake for your employer. Your employer is responsible for ensuring such checks as are necessary have been carried out. This letter confirms your right of access to conduct research through **Nottingham University Hospitals NHS Trust** for the purpose and on the terms and conditions set out below. This right of access commences on **22/02/2012** and ends on **30/09/2013** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

You are considered to be a legal visitor to **Nottingham University Hospitals NHS Trust** premises. You are not entitled to any form of payment or access to other benefits provided by this organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through **Nottingham University Hospitals NHS Trust**, you will remain accountable to your employer **Nottinghamshire Healthcare NHS Trust** but you are required to follow the reasonable instructions of your nominated manager in this NHS organisation or those given on her behalf in relation to the terms of this right of access.

We are here for you

Nottingham University Hospitals NHS

NHS Trust

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with **Nottingham University Hospitals NHS Trust** policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with **Nottingham University Hospitals NHS Trust** in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on **Nottingham University Hospitals NHS Trust** premises. Although you are not a contract holder, you must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of a contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

Nottingham University Hospitals NHS Trust will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

If your circumstances change in relation to your health, criminal record, professional registration or any other aspect that may impact on your suitability to conduct research, or your role in research changes, you must inform the NHS organisation that employs you through its normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely

Sue Barklie
Research Manager

cc: HR department of the Nottinghamshire Healthcare NHS Trust

We are here for you

From: Brindley Christina (Trent CLRN) [mailto:Christina.Brindley@nuh.nhs.uk]

Sent: 13 February 2012 10:03

To: Bryan Moreton

Cc: Victoria Tew

Subject: RE: Letters of Access (9227)

Hi Bryan

If the psychologist is only attending at NUH then a letter of access is only required at NUH. If she is required to attend SFH, then we would require a LoA there too. I will require a copy of her signed and dated CV to add her to the research team, with a covering email.

You will then receive two letters: one will be the letter of access, and the other will be an amendment approval letter for the addition of a researcher. Please ensure both are in place before the psychologist commences any research activity.

The research passport will need validating by one of my managers here at NUH who will be able to issue the letter of access, so please let me know if I can help with organising this, once the details are completed by the University and HR first.

Many thanks in advance.

Kind regards
Christina

Christina Brindley
Lead Network Research Management & Governance Facilitator
Trent Comprehensive Local Research Network

A new IT system to support CSP across the NHS is being rolled out by the NIHR Clinical Research Network. You may experience some delays to our service whilst the new system beds in and we apologise to anyone affected. We want to assure you that all those involved are working hard to ensure that full service is restored as soon as possible.

Nottingham Integrated Clinical Research Centre
Nottingham University Hospitals NHS Trust

Queen's Medical Centre Campus
C Floor, South Block
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Nottingham
NG7 2UH

Tel: 0115 9249924 extension 70641
Fax: external 0115 849 3295 Internal 35295

Trent CLRN website: http://www.crncc.nihr.ac.uk/about_us/ccrn/trent/
Trent CLRN inbox: [nuhnt.trentclrn@nhs.net]nuhnt.trentclrn@nhs.net

From: Bryan Moreton [mailto:Bryan.Moreton@nottingham.ac.uk]
Sent: 09 February 2012 09:42
To: Brindley Christina (Trent CLRN)
Cc: Victoria Tew
Subject: Letters of Access (9227)

Hi Christina,

We would like a psychologist to conduct some of the QST at City Hospital for my study (9227) to help Maggie. She has applied for a letter of access from NUH to conduct the research. However, I just wanted to check she wouldn't need anything else.

I remember you previously said regarding QST that '*Letters of access are only required if you physically need to be at a GP practice for any reason related to the research.*' That would imply that she only needs one from NUH and not from the PCTs for the GP patients. However, I just wanted to check whether she would need one from SFH. I figure it is not needed, but it is always worth checking (especially seeing as Maggie and I have a LOA from SFH).

Thank you,
Bryan

Appendix 3

All ethical documentation relevant to Studies 1 and 3 of this thesis research: final approval letters and approval details from Comprehensive Local Research Network (CLRN)

Moreton Bryan

From: Brindley Christina (Trent CLRN) [Christina.Brindley@nuh.nhs.uk]
Sent: 17 December 2012 15:24
To: Bryan Moreton
Subject: RE: Update re amendment to 57488

My apologies as I should have been quicker and completed it last week. Non-substantial amendments are classified as notifiable (requiring up to 35 days to review) or non-notifiable (implementable immediately). As this amendment included a new document (poster) and changes which I wanted to notify Trusts of to approve, I have reviewed the amendment and requested the letters/emails. Should you be missing any approval letters, please let me know. In terms of paperwork, I have completed the 35 day review email below, (from the day you submitted the amendment) just in case any letters are delayed.

Dear Bryan

Re: 57488 – Measures of pain relevant to knee osteoarthritis - Amendment 10 (non-substantial, notifiable)

Date of Submission to REC: N/A

Thank you for submitting the above amendment. As your Lead CLRN, we have made this amendment available to each participating NHS Trust. As such, local governance review is now under way at each site that has issued NHS Permission. Sites that have not yet issued NHS Permission (if applicable) have also been notified of the amendment and will consider it as part of their overall governance review.

If applicable, please ensure you send copies of your regulatory approval(s) (REC, MHRA and other supporting documents) to this email address or through the IRAS document submission. We will make these available to all participating sites.

Trusts within England have 35 calendar days to undertake their local governance review. Accordingly, subject to the three conditions below, you will be able to implement the amendment on **04/01/2013**, at all sites already in receipt of NHS Permission:

- You may not implement this amendment until and unless you receive, and forward to us, all required regulatory approvals (where applicable)
- You may not implement this amendment at any site which informs you that they require additional review time, until they notify you that this review has been satisfactorily completed.
- You may not implement this amendment at any site that withdraws its NHS Permission.

NB: you may only implement changes that were described in the amendment notice or letter.

If you receive your regulatory approvals after this date, and submit the document(s) to us, you may then immediately implement at all sites in England that have NHS Permission in place and that have not requested addition review time, or withdrawn NHS Permission.

As it is the responsibility of each individual NHS Trust in England to notify you if you may not locally implement the amendment, you are not required to wait for receipt of the Notification of Continued NHS Permission from an NHS Trust in England in relation to the amendment before you may implement on the above date.

Please note that as Chief Investigator, it remains your responsibility to ensure the PIs at each of your sites (if applicable) are informed of this amendment.

Please contact me if you require any further assistance.

Kind regards

Christina

Christina Brindley
Lead Network Research Management & Governance Facilitator
Trent Comprehensive Local Research Network

Nottingham Health Science Partners
Nottingham University Hospitals NHS Trust
Queen's Medical Centre Campus
C Floor, South Block
Derby Road
Nottingham
NG7 2UH

Tel: 0115 9249924 extension 70641
Fax: external 0115 849 3295 Internal 35295

Email: christina.brindley@nuh.nhs.uk
Trent CLRN website: http://www.crncc.nihr.ac.uk/about_us/ccrn/trent/
Study documentation and enquiries - Trent CLRN inbox: nuhnt.trentclrn@nhs.net

PLEASE NOTE: we will be operating a limited service from 21 December until 2 January.

On behalf of all of us at Trent CLRN, we would like to wish you a very Merry Christmas and a Happy New Year!

From: Bryan Moreton [mailto:Bryan.Moreton@nottingham.ac.uk]
Sent: 17 December 2012 15:11
To: Brindley Christina (Trent CLRN)
Subject: RE: Update re amendment to 57488

Hi Christina,

Thank you for sorting that out quickly as always.

Best,

Bryan

From: Brindley Christina (Trent CLRN) [mailto:Christina.Brindley@nuh.nhs.uk]
Sent: 17 December 2012 11:50
To: Bryan Moreton
Subject: Update re amendment to 57488

Hi Bryan

Just to let you know I have today requested the approvals for the most recent non-substantial amendment (amendment 10) at the current approved Trusts, except NUH.

Kind regards
Christina

Christina Brindley
Lead Network Research Management & Governance Facilitator
Trent Comprehensive Local Research Network

Nottingham Health Science Partners

Sherwood Forest Hospitals NHS Trust approval email

Moreton Bryan

From: Brindley Christina (Trent CLRN) [Christina.Brindley@nuh.nhs.uk]
Sent: 19 December 2012 08:49
To: Bryan Moreton
Subject: NIHR CSP - ref 57488 - non-substantial amendment approval (SFH)

Hi Bryan

Please see below the acknowledgement that Sherwood Forest Hospitals NHS FT are happy for you to implement this amendment.

Kind regards
Christina

Christina Brindley
Lead Network Research Management & Governance Facilitator
Trent Comprehensive Local Research Network

Nottingham Health Science Partners
Nottingham University Hospitals NHS Trust
Queen's Medical Centre Campus
C Floor, South Block
Derby Road
Nottingham
NG7 2UH

Tel: 0115 9249924 extension 70641
Fax: external 0115 849 3295 internal 35295

Email: christina.brindley@nuh.nhs.uk
Trent CLRN website: http://www.crncc.nihr.ac.uk/about_us/ccrn/trent/
Study documentation and enquiries - Trent CLRN inbox: nuhnt.trentclrn@nhs.net

PLEASE NOTE: we will be operating a limited service from 21 December until 2 January.

On behalf of all of us at Trent CLRN, we would like to wish you a very Merry Christmas and a Happy New Year!

From: Samantha Jones - Research Nurse Team Leader -SFH-KMH [mailto:Samantha.Jones@sfh-tr.nhs.uk]
Sent: 18 December 2012 16:50
To: Brindley Christina (Trent CLRN)
Cc: Kramer Guy - Evaluation & Monitoring Assistant - SFH-KMH
Subject: RE: NIHR CSP - ref 57488 - non-substantial amendment for approval (SFH)

Dear Christina,
Thank you for the information regarding the non-substantial amendment for this study. Please accept this email as our acknowledgment of our receipt of the information.

Kramer – please can you print this off and add it to the study file.

Thanks
Sam

Mrs Sam Jones
Research Nurse Team Leader
Evaluation, Audit & Research Dept
Research & Development Office

1

NHS Derby City and Derbyshire County Primary Care Trusts approval letter

Derby Hospitals NHS
NHS Foundation Trust

RESEARCH & DEVELOPMENT OFFICE

Royal Derby Hospital
Uttoxeter Road
Derby
DE22 3NE

Tel: 01332 340131
Minicom: 01332 254944
www.derbyhospitals.nhs.uk

☎**Please telephone on**: 01332 787223
Fax No: 01332 724714
E-mail: mays.jawad1@nhs.net

19th December 2012

Dr Bryan Moreton
Institute of Work Health and Organisations
University of Nottingham
Nottingham
NG8 1BB

Dear Dr Moreton

Re: Measures of Pain Relevant to Knee Osteoarthritis

Ref: DSCPCT/2011/023 & DCPCT/2011/009
IRAS: CSP: 57488

I acknowledge the receipt of your amendment dated 07.12.12 enclosing the following revised documentation for the above study

- Covering email regarding amendment 10 (non-substantial), 07/12/2012
- Poster, v1.0, 09/11/2012
- Participant invite letter: Study 2, v7, 29/11/2012
- Participant information sheet: Study2, v8, 29/11/2012
- Participant consent form: Study 2, v8, 29/11/2012

I have reviewed the revised documents on behalf of Derbyshire County and Derby City PCT and can confirm that there are no issues. You may therefore use the above documents with PCT approval.

Please do not hesitate to contact any member of the Research and Development staff if you feel we can be of assistance.

Yours sincerely,

Mays Jawad
Research Management and Governance Manager
Research & Development Department

This amendment has been reviewed by Christina Brindley, TRENT CLRN

NHS Nottingham City Primary Care Trust, NHS Nottinghamshire County Primary Care Trust and County Health Partnerships approval email

Moreton Bryan

From: Pearson Emma [Emma.Pearson@nottshc.nhs.uk]
Sent: 20 December 2012 12:00
To: Bryan.Moreton@nottingham.ac.uk
Cc: christina.brindley@nuh.nhs.uk; 'TRENTCLRN (NOTTINGHAM UNIVERSITY HOSPITALS NHS TRUST)' (NUHNT.TRENTCLRN@nhs.net); sponsor@nottingham.ac.uk
Subject: Amendment 10 CHP, NCPCT and NCoPCT
Attachments: NIHR CSP - ref 57488 - non-substantial amendment for approval

Resent to include County Health Partnerships.

Dear Prof Morton

Title: Measures of pain relevant to knee osteoarthritis
CSP ref: 57488
REC ref: 10/H0403/70
Amendment 10 (non-substantial)

Please accept this email as confirmation of continuing NHS permission for this amendment which has been received by Nottinghamshire Healthcare NHS Trust's R&D Department on behalf of County Health Partnership's, NHS Nottingham City and NHS Nottinghamshire County and can now be implemented.

Please contact us using the contact details below if you require any further information.

Kind regards

Emma Pearson
Research Governance Facilitator

Nottinghamshire Healthcare NHS Trust
Institute of Mental Health
University of Nottingham Innovation Park
Triumph Road
Nottingham
NG7 2TU

Tel: 0115 748 4320
Mobile: 07919 144382
Email: emma.pearson@nottshc.nhs.uk

NHS Bassetlaw Primary Care Trust approval letter

NHS
Bassetlaw

Retford Hospital
North Road
Retford
Nottinghamshire
DN22 7XF

Tel: 01777 274400
Fax: 01777 710535

www.bassetlaw-pct.nhs.uk

Dr Bryan Moreton
Research Fellow
University of Nottingham
Institute of Work health and Organisation
International House
Jubilee Campus
Nottingham
NG8 1BB

DATE 19/12/12

Dear Dr Moreton

Ethics Reference Number: 10/H0403/70 **Study ID:** **57488/T**

Project Title: Measures of pain relevant to knee osteoarthritis

UKCRN portfolio ID: 9227

Thank you for submitting the above project to Bassetlaw PCT. The project has now been given Organisational Approval by:

Mr Andrew Beardsall, R & D Lead, on behalf of Bassetlaw PCT

This now includes the amendments to the study as made
Amendment 1 (minor) 07/10/2010 (REC acknowledged 14/10/2010)
Amendment 2 (minor) 27/10/2010 (REC acknowledged 16/11/2010)
Amendment 4 (minor) 17/12/2010 (REC acknowledged 12/01/2011) [There is not an amendment 3, as REC incorrectly labelled amendment 3 as amendment 4].
Amendment 5 (substantial) 21/04/2011 (REC approved 12/05/2011)
Amendment 6 (substantial) 26/08/2011 (REC approved reissue 15/09/2011
Minor amendment (amendment 8) 28/06/2012
Minor amendment 10 (non-substantial), 07/12/2012
Although Organisational approval has been given for this study it does not guarantee that independent contractors such as GPs, dentists, optometrists and community pharmacists will be able to take part in your study.

Conditions of approval
Please note that approval for this study is dependent on full compliance with the following. To that end, please complete and return the form attached to this letter confirming your acceptance of these terms and conditions:

- You are required to ensure that all information regarding patients or staff remains secure and **strictly confidential** at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (***http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf***) and the Data Protection Act (1998). Furthermore, you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.
- You must not hold person identifiable data on portable media unless it is encrypted. Protecting data files with passwords does not constitute encryption
- To complete yearly/final reports as requested, and to feedback study findings to the Research and Development Department and participants (as appropriate)
- To endeavour to publish and/or disseminate research findings on completion of the project
- To inform the Research and Development Department of any changes that occur, e.g. amendments to approved documentation, project not started for any reason, change in personnel etc
- That you inform the Research and Development Department which GP Practices you have recruited to your study from Bassetlaw PCT (where applicable)
- That you inform the Research and Development Department of all serious adverse incidents[1] in accordance with Trust Policy and/or Legal requirements (e.g. Sponsor, MHRA). This is in addition to the reporting of serious or unexpected adverse events and adverse drug reactions (which may affect the conduct and continuation of the study) to the approving research ethics committee
- That you are aware of and comply with the PCT Research and Development Policies and Best Practice Guidance
- That you agree to cooperate with a Research Governance Audit of the project if requested by the Research and Development Department
- That you have read and agree to abide by the Research Governance Framework (RGF) for Health and Social Care (second edition 2005)

The *Research Governance Framework for Health & Social Care* sets out the responsibilities of all those involved in research in order to enhance the ethical and scientific quality of health research and to safeguard patients and the public. The lead investigator and all involved in the research have a responsibility to comply with Research Governance.

Full details can be found in the RGF document available at www.dh.gov.uk or via the Research and Evaluation Department.

Yours sincerely,

Andrew Beardsall
Head of Quality

Copy to Trent Comprehensive Local Research Network

Appendix 4

Nottingham University Hospitals NHS Trust

The University of Nottingham

Arthritis Research UK

Providing answers today and tomorrow

Evaluation of questionnaire measures for patients with osteoarthritis of the knee

Chief Investigator: Dr Bryan Moreton
Co-investigators: Prof. Nadina Lincoln, Dr David Walsh, Prof. Michael Doherty, Prof Brigitte Scammell
Sponsor: University of Nottingham

INFORMATION SHEET

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the University of Nottingham is doing the research, how your information will be used, what the study will involve and the potential benefits and risks. Take your time to read the following information and feel free to talk to others about the study if you wish. Please, ask us if there is anything that is not clear.

WHY IS THIS STUDY BEING DONE?

There are already many treatments that can help people with pain, but pain remains the commonest problem of people with arthritis. Pain can be very complex, both in how it feels and how it affects people. Different treatments can help pain in different ways, but can also sometimes cause problems of their own. More research is needed to gain a better understanding of how pain affects people and things that might cause or improve arthritis pain. Researchers in the Arthritis Research UK Pain Centre at the University of Nottingham are carrying out a number of research studies to identify different mechanisms that contribute to arthritis pain, and what people think and feel about it. This particular study aims to advance our understanding of existing measures relevant to the mechanisms of osteoarthritis knee pain and to examine the factors associated with the experience of pain. Gaining a better understanding of the assessment of pain will help us develop treatments to improve quality of life.

WHY HAVE I BEEN INVITED?

We are inviting people with osteoarthritis that causes pain in one or both knees. You have been invited either because your doctor **(or another healthcare professional responsible for your care)** thinks that you may be able to help us, or because you have previously indicated that you would be happy to be contacted about research studies such as this.

DO I NEED TO TAKE PART?
NO IT IS ENTIRELY VOLUNTARY.

It is up to you to decide whether to join the study. You do not have to be involved in this research if you do not want to. If you decide that you do not want to take part, you do not have to give a reason for this. If you agree to take part, we will ask you to complete and sign the consent form included in the letter and return it with the questionnaires in the pre-paid envelope.

WHAT ARE WE ASKING YOU TO DO?

We are seeking volunteers with osteoarthritis of the knee to take part in our study. We have sent you a booklet of questionnaires about your pain, your arthritis and its treatment, how you manage it, and about your general health and well-being. We estimate that the questionnaires may take people up to 60 minutes to complete, but you will be able to complete them at your own pace. We would like you to complete as much of the questionnaires as you can and then return them in the pre-paid envelope provided. **Please note that questions about your pain are referring to your knee pain caused by osteoarthritis.**

You may also be invited to take part in Quantitative Sensory Testing (QST). QST is a non-invasive test (i.e., no needles are used) that measures how sensitive nerves are by recording the smallest force that is required for pressure to be felt as pain. If you participate, during the test, a researcher will press a blunt probe onto certain parts of your body. The probe consists of a rod with an end the size of a 5p piece, mounted in a hand held device connected to a computer. The force with which the probe is pressed onto your skin will be gradually increased until you indicate, by pressing a button, as soon as the sensation has changed from pressure to pain. At that point, the researcher will immediately take the probe off your skin. The sensation of pain will be mild and temporary in nature. The researcher will press the probe on your knees, legs, and another site such as the front of your chest. Each region will be tested three times with short rest periods between. Before starting the procedure, we will familiarise you with the test by applying the probe to one of your hands so that you will know what to expect and how to respond as soon as you feel any pain. You will be able to indicate at any point if you do not wish to continue. The researcher administering the QST will also go over any questions from the questionnaires that were not answered.

Before taking part in QST a researcher will contact you by telephone to discuss QST with you, answer any questions that you may have, ensure that you are suitable to take part and, if you are, arrange a time that is convenient for you to attend Academic Rheumatology, Clinical Sciences Building, City Hospital, Nottingham. If you have already taken part in QST in another study conducted by the Arthritis Research UK Pain Centre (University of Nottingham) then you may not be required to participate again.

We are also seeking your permission to look in your hospital notes, if relevant, for other information that may be helpful to the research, for example, medical history and medicines that have been prescribed. Finally, **you may be invited** to complete the questionnaires again at three and six months after initial assessment to examine change over time. This will be conducted entirely through the post**, but we may telephone you to remind you of this**.

If you would prefer not to take part in the **QST** and/or the three and six month follow-up assessments, but you are happy to complete the **initial set of** questionnaires, we would be very grateful for your participation. You will be able to indicate your preference**(s)** on your consent form.

Please feel free to contact us by telephone or by post if you would like a researcher to visit you at home to help you complete the questionnaires.

EXPENSES AND PAYMENTS

All travel expenses will be fully reimbursed for attending Academic Rheumatology. There will however be no payment for taking part in the study.

WHAT ARE THE BENEFITS OF TAKING PART?
Taking part in our study means that you may possibly help people with arthritis in the future, as information may be used to develop new treatments and improve management of arthritis. We do not expect you to directly gain from taking part.

WHAT ARE THE POSSIBLE DISADVANTAGES OF TAKING PART?
Taking part in this study does not require you to take any new treatments, nor to change the way you manage your arthritis. We appreciate that taking part will use your time and may therefore be inconvenient. Some of the questions from the questionnaires cover topics that may be considered sensitive or embarrassing, but all information provided will be kept strictly confidential. **If you take part in the QST, then you will feel slight discomfort in the area where the probe is placed. However, the feeling will be temporary and a**ny aspect of your involvement in the study can stop at any time if you do not wish to continue.

WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. Information will not be used or disclosed in a form that might identify you without your consent.

WHAT WILL HAPPEN IF I DON'T WANT TO CARRY ON WITH THE STUDY?
Your participation is voluntary and you are free to withdraw at any time, without giving any reason by **either informing the researcher administering the QST or** phoning the study contacts on 0115 846 6545. This will not affect the standard of care you receive, and your legal rights will not be affected. If you withdraw then the information collected so far cannot be erased and this information may still be used in the project analysis.

WHAT WOULD WE DO WITH THE INFORMATION THAT YOU GIVE US?
The questionnaire and **QST** data will be transferred to an electronic database and used in analysis. The electronic files will be stored on password protected computers and storage devices (e.g., CDs). The questionnaire sheets will be stored at the University of Nottingham in locked cabinets for seven years before being destroyed. We will store personal information such as names in a separate file from the questionnaire sheets, and we will assign an anonymous identity code to all data. Only the researchers and the authorised representatives of the study sponsor will have access to your personal data. Your personal details will not be provided to anyone else, or used for any purpose other than our research. They will be destroyed after it is no longer necessary to contact you.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?
The information that you provide will help us refine the assessment of pain in people with osteoarthritis. The results of the study may be presented to other researchers, at meetings and through publication in scientific journals. A summary of the findings will also be provided to Arthritis Research UK, which is funding this study. We will ensure that it will not be possible for anyone to identify you from the published findings of the study.

We will put a summary of the results on our website http://www.nottingham.ac.uk/psincentre when the study is finished. If you ask the researcher, we would be happy to send you a copy of the results when they are available.

WHO IS ORGANISING AND FUNDING THE STUDY?
This research is being organised by the University of Nottingham and is being funded by Arthritis Research UK.

WHO HAS REVIEWED THE STUDY?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Nottingham Research Ethics Committee.

WHAT IF THERE IS A PROBLEM?
If you have concerns about any aspect of the way you have been treated during the course of the study, please discuss them with the researcher **administering the QST** or **the** Chief Investigator. If you wish to raise your concerns with someone who is independent of the research team, please contact the Nottingham University Hospitals PALS Department on 0800 183 0204.

FUTURE CONTACT
This study is a part of a larger programme of research into arthritis pain. We would be grateful if you could indicate on the consent form whether you would be willing for us to contact you about other parts of our research in the future. **Please note that the boxes on the consent form need to be initialled rather than ticked. It is important that you sign and date the consent form and initial rather than tick the boxes.**

If you have any further questions about this study, or wish to contact the study sponsors, please contact:

Dr Bryan Moreton (Chief Investigator)
University of Nottingham
Institute of Work, Health and Organisations
International House
Jubilee Campus
Wollaton Road
Nottingham, NG8 1BB
Telephone: 0115 846 6545
Email: bryan.moreton@nottingham.ac.uk

Thank you for taking the time to read this invitation

Appendix 5

Instructions for QST patients

The idea of these tests is to look at pain thresholds in people with OA. We aren't looking at how much pain you can tolerate, simply at what point you start to feel pain. The pain you feel will only be fleeting, as the test will be stopped as soon as you indicate that you have started to feel pain.

You will hold this push button in your dominant hand and I will start to apply a graded pressure on your finger nail bed.

You will feel pressure as the probe is pressed down and the pressure will be gradually increased.

As soon as the pressure starts to change to pain, you should press the button and I will withdraw the probe.

The first test is on the finger nail and is really just a practice to let you know how it feels.

Then I will do the same on other parts of your body. Specifically the sternum, around the knee joint and on the lower leg.

At each site I will take 3 readings with a few seconds in between.

Between each site there will be a 2 minute break.

The computer records your pain threshold of each test and this will be compared with other volunteers who also have osteoarthritis in their knee.

Also in a week's time we can see if your results have changed from the first set of tests.

If, for any reason, you want to stop, let me know straight away.

Do you have any questions?

Appendix 6

Nottingham University Hospitals NHS Trust

The University of Nottingham

Arthritis Research UK

Providing answers today and tomorrow

CONSENT FORM
(Version 6
26.08.2011)

Evaluation of questionnaire measures for patients with osteoarthritis of the knee

Chief Investigator: Dr Bryan Moreton
Co-investigators: Prof. Nadina Lincoln, Dr David Walsh, Prof. Michael Doherty, Prof. Brigitte Scammell
Sponsor: University of Nottingham
REC ref: 10/H0403/70

Please initial box

1. I confirm that I have read and understand the information sheet version number **6** dated **26.08.2011** for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐

3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐

4. I agree to take part in the above study. ☐

5. (Optional) I agree to take part in Quantitative Sensory Testing. ☐

6. (Optional) I agree to take part in the three and six month follow-up assessments. ☐

7. (Optional) I agree to being contacted in the future about other research studies. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes
[EITHER]PLEASE RETAIN THIS COPY FOR YOUR RECORDS[OR]PLEASE RETURN THIS COPY WITH YOUR QUESTIONNAIRES IN THE PRE-PAID ENVELOPE

Study 2

The University of Nottingham

EVALUATION OF QUESTIONNAIRE MEASURES FOR PATIENTS WITH OSTEOARTHRITIS OF THE KNEE

Protocol Version 3
26.08.2011

Short title: Measures of pain relevant to knee osteoarthritis

REC reference: 10/H0403/70

Trial Sponsor: University of Nottingham

Funding Source: Arthritis Research UK

STUDY PERSONNEL AND CONTACT DETAILS

Sponsor:
Contact name

University of Nottingham
Mr Paul Cartledge
Head of Research Grants and Contracts
Research Innovation Services
King's Meadow Campus
Lenton Lane
Nottingham
NG7 2NR

Chief Investigator:

Dr Bryan Moreton,
Institute of Work, Health and Organisation
Jubilee Campus, Wollaton Road,
Nottingham, NG8 1BB
Phone: 0115 846 6545
Fax: 0115 846 6625
Email: bryan.moreton@nottingham.ac.uk

Co-investigators

Professor Nadina Lincoln,
Institute of Work, Health and Organisation
Jubilee Campus, Wollaton Road,
Nottingham, NG8 1BB
Phone: 0115 951 5315
Fax: 0115 846 6625
Email: nadina.lincoln@nottingham.ac.uk

Dr David Walsh
Room A19, Academic Rheumatology,
Clinical Sciences building
Nottingham City Hospital,
Nottingham, NG5 1PB
Phone: 0115 823 1757
Email: david.walsh@nottingham.ac.uk

Professor Michael Doherty
Room A24, Academic Rheumatology
Clinical Sciences Building
City Hospital
Nottingham, NG5 1PB
Phone: 0115 823 1756
Fax: 0115 823 1757
Email: michael.doherty@nottingham.ac.uk

Professor Brigitte Scammell
Nottingham University Hospitals NHS Trust
QMC campus
Derby Road
Nottingham
NG7 2UH
Phone: 0115 823 1120
Fax: 0115 823 1118
Email: b.scammell@nottingham.ac.uk

Study Coordinating Centre

Institute of Work, Health and Organisations
University of Nottingham
Jubilee Campus, Wollaton road,
Nottingham, NG8 1BB

TABLE OF CONTENTS

SYNOPSIS

Title	Evaluation of questionnaire measures for patients with osteoarthritis of the knee
Acronym	N/A
Short title	Measures of pain relevant to knee osteoarthritis
Chief Investigator	Dr Bryan Moreton
Objectives	The aim is to improve our understanding of the assessment of pain experience in patients with osteoarthritis (OA) of the knee. The current study will be divided into two parts. In Study 1, we will analyse existing questionnaires relevant to the mechanisms and therapeutic targets of knee OA to establish discrete dimensions that discriminate between the different mechanisms of pain. On the basis of this analysis, we will refine the questionnaires to maximise their sensitivity to knee OA. In Study 2, we will seek to confirm the factor structure identified in the questionnaires in Study 1 and explore potential mediator and moderator variables between pain and quality of life using the refined measures. We will also evaluate Quantitative Sensory Testing (QST) as a predictor of OA knee pain **in Study 2**. A QST sub-study in Study 1 will seek to determine the acceptability, reliability, and required sample size for the QST planned in Study 2.
Study Configuration	Multicentre, cross sectional cohort.
Setting	Hospital clinics**, GP surgeries** and participants' residence.
Sample size estimate	Sample size calculations were based on Rasch Analysis, because this will be the primary form of data analysis in both Study 1 and Study 2. Linacre (1994) suggests that a sample size of 250 participants would provide a high degree of confidence (99% and above) that the item calibrations are stable (i.e., at least within 0.5 logit). Thus we decided to recruit 250 participants in Study 1 and Study 2 (total n = 500). Study 2 also aims to explore potential mediator and moderator variables between pain and quality of life using the Rasch scaled Questionnaires from Study 1. Two hundred and fifty participants will be sufficient for this multiple regression analysis. Specifically, only 145 participants would be required to have 90% power (α = 0.05) to test a model with 10 predictor variables and a moderate effect size (f^2 = 0.15).
Number of participants	Five-hundred knee OA patients (250 in Study 1, 250 in Study 2). However, we plan to send out twice the number of invitations to

	participate in study 1 because we anticipate a response rate of approximately 50% **based on our previous studies. No limits will be placed on the number of invitations in study 2 because it is difficult to predict the response rate from the various different sources of recruitment (see below for details). The invitations will be sent out in a staggered fashion to avoid sending out more than is needed.** Any addition participants (i.e., more than 250 participants in Study 1 or Study 2) will be included in the analysis.
Eligibility criteria	The participants **in Study 1** will have OA of the knee defined and scored radiologically using European League Against Rheumatism (EULAR) criteria and line atlas. They will also report knee pain. **Participants in Study 2 will require a clinical diagnosis of knee OA and accompanying pain, but they will not be required to have radiographic evidence.** All participants must provide informed consent – this can be implied in Study 1 by completion of the questionnaire set.
Description of interventions	The participants in both Study 1 and Study 2 will be invited to complete a series of questionnaires assessing pain perception, anxiety, depression, fatigue, illness belief, self-efficacy, coping and quality of life. Estimated completion time is approximately **1** hour, but participants will complete the questionnaires in their own home at a pace that is convenient for them. A pre-paid envelope will be provided to return the questionnaires after completion. Twenty participants from Study 1 will be recruited to take part in a QST sub-study. Pain pressure thresholds (i.e., first sensation of pain) will be assessed using an electronic algometer. Testing will take place in hospital clinics. The test is non-invasive and patients will experience relatively little discomfort. We estimate that the testing procedure will take approximately 60 minutes. The results of this study will inform the QST planned in Study 2. Participants from Study 2 **may** be invited to complete the questionnaires again at three and six months after initial assessment to examine change over time **and may** also be invited to participate in **QST. The procedure will be based on the sub-study.**
Duration of study	Two years.
Outcome measures	The primary outcome for both Study 1 and Study 2 will be scores on the questionnaire set: • McGill Pain Questionnaire to assess pain • Osteoarthritis Research Society International OA pain assessment tool (knee) to assess pain • PainDETECT which has been designed for neuropathic elements of patients' pain • Self-Report Leeds Assessment of Neuropathic Signs and Symptoms to assess neuropathic elements of patients' pain

	• Speilberger State-Trait Inventory to assess anxiety • Beck Depression Inventory to assess depression • Fatigue Severity Scale to assess fatigue • Pain Self-Efficacy Questionnaire a measure of the extent to which patients believe they can control their pain • Chronic Pain Acceptance Questionnaire 20 item version to assess acceptance • Pain Coping Belief Scale to measure belief of control over pain • Pain Coping Strategies Questionnaire to measure coping • Arthritis Helplessness Index a measure of how well patients cope with arthritis • Illness Perceptions Questionnaire Revised a measure of beliefs about illness • SF-36 to measure quality of life A secondary outcome for the sub-study (of Study 1) and Study 2 only will be scores from the Quantitative Sensory Testing.
Statistical methods	The data from Study 1 **(including the sub-study)** will be analysed before conducting Study 2, because it will inform the latter investigation. The following methods will be used: • Rasch Analysis to refine the questionnaires • Person Separation Index as a measure of internal consistency • Factor analysis to establish discrete dimensions • Inter- and intra- individual and intra-examiner reliability of pain pressure threshold measurements • Mean, standard deviation, and 95% confidence intervals of the pain pressure thresholds. • Statistical tests of differences between different QST sites for the pain pressure thresholds The Rasch scaled questionnaire set will be given to the participants in Study 2. The analysis used in Study 1 will be repeated to confirm the factor structure of the questionnaires. In addition, **a Delphi Process is planned to establish mechanistic dimensions in the questionnaires.** Test-retest reliability will be assessed for the data provided at three and six months; Kappa Coefficients will be calculated for individual items and Bland and Altman plots or Intraclass Correlations for total scores. Finally, Multiple Regression will be performed to establish mediator and moderator variables between pain and quality of life measures.

ABBREVIATIONS

AHI	Arthritis Helplessness Index
BDI-II	Beck Depression Inventory II
CPAQ	Chronic Pain Acceptance Scale 20 item version
CRF	Case Report Form
EULAR	European League Against Rheumatism
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IPQ-R	Illness Perception Questionnaire Revised
S-LANSS	Self-report Leeds Assessment of Neuropathic Signs and Symptoms
MPQ	McGill Pain Questionnaire
NHS	National Health Service
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
BPCQ	Pain Coping Belief Scale
PCSQ	Pain Coping Strategies Questionnaire
PSEQ	Pain Self Efficacy Questionnaire
QMC	Queens Medical Centre
REC	Research Ethics Committee
R&D	Research and Development department
SF-36	Short Form 36
STAI	Spielberger State Anxiety Index
QST	Quantitative Sensory Testing

STUDY BACKGROUND INFORMATION AND RATIONALE

It has been estimated that OA affects approximately 8.5 million people in the UK alone (http://www.nhs.uk/conditions/osteoarthritis/Pages/Introduction.aspx). It is characterised by damage to joints and inflammation of the surrounding tissue, which often results in chronic pain. OA of the knee in particular has been shown to be one of the most commonly reported causes of disability in older adults (Gucionene et al., 1994). In addition to causing pain and physical restrictions (Yelin, 1992), OA influences psychosocial well-being and correlates with emotional distress and depression (Bruce, 2000). There is no cure for the disease and so further research is essential to manage the condition and improve patients' quality of life. This study aims to advance our understanding of the assessment of pain by analysing existing questionnaires relevant to mechanisms and therapeutic targets in OA knee pain. We also aim to explore the psychological factors associated with pain experience.

Current pain questionnaires are designed as outcome tools, which have clinically important dimensions. For example, the Osteoarthritis Research Society International (OARSI) OA pain assessment tool (knee) provides a total pain score, but the items can also be grouped according to constant pain and intermittent pain which are clinically useful dimensions (Hawker et al., 2008). However, for target identification studies, it is necessary to discriminate between the various mechanistic components of the complex pain phenomenon. We plan to establish mechanistic dimensions in existing questionnaires by analysing responses provided by knee OA patients in the local community.

Pain shares a close relationship with emotional distress and in particular depression (Parmelee et al., 2007). Evidence suggests that psychological factors account for a moderate proportion of the variance in pain experience. For example, Summers et al. (1988) found that measures of depression, state anxiety and trait anxiety accounted for 32% of the variance in present pain intensity as measured by the McGill Pain Questionnaire (MPQ). However, this relationship may have been underestimated if each questionnaire contains items that are inappropriate for OA. Indeed Dixon et al. (2007) recently commentated that the use of pain measures that are specific to arthritis is limited in psychosocial intervention studies. It is therefore appropriate that we intend to refine existing questionnaires to maximise their sensitivity to the psychological components of pain experience in people with OA. We will use these refined measures to explore potential mediators and moderators between pain and quality of life to improve our understanding of the psychological factors associated with pain experience.

An alternative pain assessment tool to questionnaires is offered by Quantitative Sensory Testing. There are two basic techniques (Shy et al., 2003):

- The method of limits – participants are presented with a gradually changing stimulus (e.g., vibrations) until they can feel it.
- The method of levels – participants are presented with predetermined levels of stimulus and are required to make a forced choice about whether they can feel it.

The data obtained from participants is used to assess sensory thresholds, which can be contrasted between different individuals or for different parts of the same individual (e.g., affected knee and healthy knee). Studies have shown that OA patients often exhibit over sensitivity to painful stimulation in affected areas. For example, Dieppe et al. (2008) found that 19/28 OA knee patients presented with thermal allodynia, which was severe in four cases. Interestingly however, patients also had a lower sensitivity to touch in their affected knee compared with their contralateral knee. Similarly, Kosek and Orderberg (2000) found that 14 patients with painful OA of the hip presented with an increased sensitivity to innocuous warmth, pressure pain, cold pain and heat pain in their affected area. We hypothesise that Quantitative Sensory Testing could be a useful predictor tool for OA knee pain, but more research is needed with larger sample sizes to explore this possibility. Therefore, we also aim to evaluate Quantitative Sensory Testing with knee OA patients in the current study.

Gaining a better understanding of the assessment of pain experience in knee OA is important because it has the potential to facilitate the evaluation of new interventions targeting specific mechanisms of pain. This is necessary to help clinicians promote their use in the National Health Service (NHS), which would augment treatment options and may also improve knee OA patients' quality of life.

STUDY OBJECTIVES AND PURPOSE

PURPOSE

The current study is part of an ongoing multidisciplinary research programme investigating the mechanisms of OA knee pain to develop and improve treatment. There are four main aims: (1) to establish mechanistic dimensions in existing questionnaires that allow discrimination between the different components of pain perception; (2) to refine existing questionnaires to maximise their sensitivity to knee OA; (3) to explore potential mediator and moderators between pain and quality of life measures; (4) to evaluate Quantitative Sensory Testing as a predictor of OA knee pain. The results of this study will be fed into future studies evaluating novel and existing interventions for pain.

PRIMARY OBJECTIVE

Study 1: To examine the psychometric properties of existing questionnaires to improve their ability to measure dimensions relevant to pain.

Study 2: To examine, using the measures refined from Study 1, the factors associated with the experience of pain.

SECONDARY OBJECTIVES

To evaluate Quantitative Sensory Testing as a predictor of OA knee pain.

STUDY DESIGN

STUDY CONFIGURATION

The study will be divided into two parts and will use a multicentre cross sectional quantitative questionnaire design. In Study 1, 250 knee OA patients will be recruited from either a cohort of patients known to Professor Doherty who have already agreed to be contacted about future research or from clinics at Nottingham University Hospitals and Sherwood Forest Hospitals. These patients will represent both urban and rural populations and a broad socioeconomic spectrum. The initial approach will be a letter inviting potential participants to take part in the study, which will be signed by either Professor Doherty or their consultant responsible for care. We anticipate a response rate of approximately 50% (based on our previous studies), so we will send out 500 invitation letters. The letters will include an information sheet, a consent form, the questionnaire set and a pre-paid envelope should they wish to take part. The consent form will contain a clause which invites participants to indicate their interest in being contacted about future research (this will also be included in Study 2). Participants in Study 1 will be told that they only need to sign the consent form if they are interested in taking part in future research. If they are not interested in being involved in future research, they will only be required to complete the questionnaires, which will be taken as implied consent. The information sheet will outline the purpose, nature and methods of the study as well as the risks, burdens and potential benefits. It will be made clear to potential participants that they do not have to participate, and if they chose to participate they can withdraw from the study at any point without providing a reason and without consequence. The potential participants will be told how their data will be treated and they will be given an opportunity to receive feedback about the results. We will request some personal details from the participants (e.g., name and telephone number) to enable us to contact them if needed. Demographic details will be recorded including age, gender and ethnicity. In addition, symptom duration and current treatment utilisation will also be documented. The participants will be given the following questionnaires to complete, which were chosen because they have been used in previous research to measure pain experience, beliefs and emotional status:

- MPQ to assess pain (Melzack, 1975)
- OARSI OA pain assessment tool (knee) to assess pain (Hawker et al., 2008)
- PainDETECT which has been designed for neuropathic elements of pain (Freynhagen, Baron, Gockel & Tolle, 2006)
- Self-Report Leeds Assessment of Neuropathic Signs and Symptoms (S-LANSS) developed to assess neuropathic elements of pain (Bennett, Smith, Torrance & Potter, 2005)
- Speilberger State-Trait Inventory (STAI) to assess anxiety (Speilberger, Gorsuch & Lushene, 1970)
- Beck Depression Inventory (BDI-II) to assess depression (Beck, Steer & Brown, 1996)
- Fatigue Severity Scale (FSS) to assess fatigue (Krupp, La Rocca, Muir-Nash & Steinberg, 1989)

- Pain Self-Efficacy Questionnaire (PSEQ) a measure of the extent to which patients believe they can control their pain (Nicholas, 1989)
- Chronic Pain Acceptance Questionnaire (CPAQ) 20 item version to assess acceptance (McCracken, Vowles & Eccleston, 2004)
- Pain Coping Belief Scale (BPCQ) to measure belief of control over pain (Skevington, 1990)
- Pain Coping Strategies Questionnaire (PCSQ) to measure coping (Rosenstiel & Keefe, 1981)
- Arthritis Helplessness Index (AHI) a measure of how well patients cope with arthritis (Nicassio, Wallston, Callahan, Herbert & Pincus, 1985)
- Illness Perceptions Questionnaire Revised (IPQ-R) a measure of beliefs about illness (Moss-Morris, Weinman, Petrie, Horne, Cameron & Buick, 2002)
- SF-36 to measure quality of life (Ware, Kosinski & Keller, 2000)

We will present the questionnaires in one of four possible orders, which will be randomly determined. As this is a lengthy set of questionnaires, the participants will be offered the choice at the mid-point stage to either continue or leave the remaining questionnaires blank. The questionnaires will be analysed within themselves and so not all participants need to complete them. The participants will complete the questionnaires at home in their own time. They will be offered the opportunity for a researcher to visit them at home and to assist with completion of the questionnaires if they wish. If the participants have not returned their information after three weeks, a reminder letter will be sent. No further action will be taken. The data will be entered into an SPSS file for analysis and checked by an independent researcher to protect against researcher effects or biases. The data from Study 1 will be analysed before starting Study 2. The analysis will focus on establishing discrete mechanistic dimensions and refining the questionnaires to maximise their sensitivity to knee OA. Poorly performing questionnaires **and individual items may** be removed from the set.

Twenty participants from Study 1 who indicated that they are happy to be contacted about future research will be recruited into a QST sub-study forming part of Study 1. A postal invitation letter will be sent to approximately 60 patients (as we expect a response rate of approximately 30%) which will include a reply slip, participant information sheet and a pre-paid envelope (a reminder will be sent to those who don't reply after three weeks). Those indicating interest in taking part will be contacted by a researcher and will complete a telephone screening to ensure eligibility to take part [eligibility exclusion criteria will be the same as Study 1]. Individuals who meet the basic criteria will be asked to choose a date and time that is convenient for them to attend Academic Rheumatology, Clinical Sciences Building, City Hospital, Nottingham. On arrival, the researcher will explain the study ensuring that the participant understands what is involved and the contents of the participant information sheet, and seek written consent. The participants will be invited to take part in QST in a clinical assessment room in Academic Rheumatology and to complete a short feedback questionnaire about the acceptability of the procedure. Pain pressure thresholds (i.e., first sensation of pain) will be assessed with an electronic pressure algometer with a laptop recording/display device and a patient switch (Somedic Sensebox). The algometer has a 1cm diameter probe, which will be

applied with graded pressure to test sites. At the time at which the participant indicates that the probe application is experienced as pain rather than pressure, the probe will be retracted immediately ceasing stimulation. The participants will be familiarised with the procedure before the start of the assessment by applying the stimulus to a learning site on one hand. This will ensure that the participants understand the nature of the stimulus and how to respond when pain is felt. The stimulus will be applied to adjacent (e.g., medial joint line, lateral joint line, patella tendon, vastus medialis, vastus lateralis) and distal (e.g., tibialis anterior, peroneus longus, medial malleolus, lateral malleolus, first metatarsophalangeal) sites to the most painful knee and one remote (e.g., lower back, shoulder, sternum) site. These were chosen on the basis of systematic review of pressure algometry studies in OA. The stimulus will be applied to each area of interest three times with intervals between and pain pressure thresholds will be recorded. Two minute rest intervals will be interspersed between sites. The researcher administering the QST will have undergone special training to assess pain pressure thresholds in human participants with a Somedic Sensebox algometer. Each participant will be asked to attend on a second occasion, one to four weeks after the first assessment, where QST will be repeated using the same protocol. In addition, the researcher will ask participants a few questions about whether their pain has changed since filling out the questionnaires in Study 1 (including a 0-10 Numeric Rating Scale for current pain intensity). Participants will be able to stop the QST testing procedure at anytime and can withdraw their consent for the sub-study. Data analysis will seek to determine the acceptability, reliability and required sample size for the QST planned in Study 2.

In Study 2, an independent cohort of 250 knee OA patients will be identified and recruited in a similar way to participants from Study 1. **They will be recruited from a cohort of patients who took part in previous studies in the Pain Centre and agreed to be contacted about future research (e.g., 10/H0408/115), clinics at Nottingham University Hospitals and Sherwood Forest Hospitals, General Practioner (GP) surgeries in the local area and from patients on the Nottinghamshire county OA hip and knee pathway.** They will be sent an invitation letter signed by either **a medical professional responsible for their care (e.g., consultant surgeon, GP, physiotherapist for those on the orthopaedic pathway) or the chief investigator of the study they previously took part in. The letter will include** an information sheet, a consent form, the refined questionnaire set and a pre-paid envelope should they wish to take part. **A reminder letter will be sent out after three weeks (if possible) to those that don't respond. We will place no limit on the number of invitations sent out, because it is difficult to predict the overall response rate from the various sources of recruitment (i.e., hospital clinics, GP surgeries, and participants in other Pain Centre Studies and pathway patients). However, recruitment will be staggered to avoid sending out too many invitations. Participants may be invited to take part in QST. They will be able to indicate on their consent form if they do not wish to take part in QST. A** researcher will telephone **those invited to participate in QST to complete a telephone screening and to** arrange **a time and date when they could attend Academic Rheumatology. The QST methodology will be informed by the sub-study and so use the same procedure. On arrival to Academic**

Rheumatology, a researcher will ensure that the participants understand what is involved in the study, the contents of participant information sheet and will remind them that they can withdraw consent at any point without providing a reason. Pain Pressure Thresholds (i.e., first sensation of pain) will be assessed using an electronic algometer with a laptop recording/display device and a patient switch (Somedic Sensebox). The 1cm probe will be applied with graded pressure at preselected test sites until pain is felt by the participant. Before starting the trial, the stimulus will be applied to a learning site (hand) so that participants can be familiarised with the process. The probe will be placed in the most appropriate regions as identified by the sub-study and will be placed in each region three times with rest internals interspersed between sites. Test sites are likely to include adjacent (e.g., medial joint line, lateral joint line, patella tendon, vastus medialis, vastus lateralis) and distal (e.g., tibialis anterior, peroneus longus, medial malleolus, lateral malleolus, first metatarsophalangeal) sites to the most painful knee and one remote site (e.g., lower back, shoulder, sternum). The patients will be asked a few questions to ascertain whether their pain has changed since completing the questionnaires. The researcher **administering the QST** will **also** go over any questions from the **questionnaire set** which were not answered. **A researcher will telephone participants who do not take part in the QST to go over any uncompleted questions. As in Study 1, the participants will be offered the opportunity for a researcher to visit them at home to help with their questionnaires.** The University of Nottingham fieldwork guidelines will be followed to ensure the safety of participants and researchers during visits. It is important to mention that participants who do not want to take part in the Quantitative Sensory Testing, but are happy to complete the questionnaires, will still be included in Study 2. **P**articipants from Study 2 **may** be invited to complete the questionnaires again at three and six months after initial assessment to analyse change over time. Participants will be able to indicate on their consent form if they are interested in taking part in the follow-up assessments. This part of Study 2 will be conducted entirely through the post **and telephone calls will be used to remind participants about follow-up assessments. It is likely that a number of participants will have undergone knee replacement surgery between completing the initial questionnaire and the follow-up assessments. These participants may still be invited to complete the follow-ups so that we can examine how sensitive the questionnaires are to change. Participants will be asked to indicate if their OA knee treatment has changed between questionnaire sets.** The questionnaire order in Study 2 will be in one of four possible orders, which will be randomised. The data will be used to confirm the factor structure identified in Study 1, to explore potential mediator and moderator variables between pain and quality of life measures and to evaluate Quantitative Sensory Testing as a predictor for OA knee pain.

STUDY MANAGEMENT

The study will be managed by the research team at the Institute of Work, Health and Organisations in collaboration with the Pain Centre – both based at the University of Nottingham. The data will be collected through completion of a series of questionnaires and Quantitative Sensory Testing. All physical data (e.g., response

sheets) will be stored in locked cabinets at the University of Nottingham for a period of seven years before being destroyed. Only the researchers and the authorised representatives of the study Sponsor will have access to personal data. Personal details will not be provided to anyone else, or used for any purpose other than our research. Each participant will be assigned an identity code, composed of the participants' initials, date of birth and a study number, to protect against transcription errors. The questionnaires will be assigned a study number before being sent to participants. An independent confidential record of the participant's name, date of birth, address, local hospital number or NHS number, and study number, will be kept to permit identification of all participants in case additional follow-up is required. This will be stored separately from the questionnaire records. Electronic data will identify participants by their identity code and will be password protected. Dr Bryan Moreton will be custodian of the data.

DURATION OF THE STUDY AND PARTICIPANT INVOLVEMENT

The majority of participants will be in the study for the duration of the outcome assessments, which we anticipate will take approximately an hour to complete. If one includes the time taken to send the information by post (and to arrange a meeting for QST in the sub-study of Study 1 and Study 2), then this will extend the time that the participants are engaged in the study. This will obviously vary according to current postal transit speed. Some participants from Study 2 will complete the questionnaire set again at three and six months after initial assessment and so these participants will be in the study for around six months.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

We aim to recruit a cross section of participants covering a broad spectrum of people with OA of the knee. **In study 1, c**ommunity participants will be identified by Professor Doherty who has a cohort of patients who have already agreed to be contacted about future research studies. Additional participants will be identified from clinics at Nottingham University Hospitals and Sherwood Forest Hospitals. **In study 2, we will recruit patients from previous studies at the Pain Centre who agreed to be contacted about future research, patients from clinics at Nottingham University Hospitals and Sherwood Forest Hospitals, patients from GP surgeries in the local area and patients on the Nottinghamshire county OA hip and knee pathway. Nottingham University Hospitals and Sherwood Forest Hospitals clinics** will include those attended rheumatology and orthopaedic specialist clinics for knee OA and rheumatology outpatients at the Queens Medical Centre (QMC). The initial approach in Study 1, the sub-study and Study 2 will be a letter inviting potential participants to take part. **The letter will be signed by a medical professional responsible for their care (e.g., consultant surgeon, GP or physiotherapist for those on the pathway), Professor Doherty for cohort patients in Study 1, or the chief investigator of the study that patients previous took part in at the Pain Centre for the sub-study and Study 2.** In Study 1 and Study 2, the letter will include an information sheet, a consent form, the questionnaire

set and a pre-paid envelope should they wish to take part. In the sub-study and Study 2 only, a meeting may be arranged to conduct Quantitative Sensory Testing. The participants in Study 1 will only be required to sign their consent form if they are interested in taking part in future research. In contrast, all participants in the sub-study of Study 1 and Study 2 will be asked to sign their consent form, because they may also be invited to take part in Quantitative Sensory Testing and in Study 2 follow-up assessments. No time limits will be placed on the participants' decision about whether to take part in the study. We will select participants to include those with different treatment experiences (e.g., pharmacological and physiotherapy) to provide a realistic sample of knee OA patients in care.

Inclusion criteria

The participants **in Study 1** will have OA of the knee defined and scored radiologically using EULAR criteria and line atlas. They will also report knee pain. **The participants in Study 2 will be required to have a clinical diagnosis of knee OA and report accompanying pain.** All participants must provide informed consent – this can be implied in Study 1 by completion of the questionnaires.

Exclusion criteria

The principal exclusion criteria of the study will be:

1. Inability to speak or understand English as they would struggle to complete the questionnaires
2. Under the age of 18 years old, because the study is aimed at legal adults
3. Joint surgery within three months prior to participation as this may affect their pain response
4. Diagnosed Rheumatoid Arthritis, Psoriatic Arthritis, Gout or any other inflammatory arthritis disorder, because the study is focussed on OA

The participants in Study 2 will also be excluded if they participated in Study 1, because this may affect their responses on the questionnaires. **Since we are unable to be sure who was invited to take part in Study 1, we have added a line to the invitation letter apologising if patients are invited more than once.**

Expected duration of participant participation

Most participants are expected to be engaged in the study for the duration of the outcome assessments (approximately an hour). Some participants from Study 2 will complete the questionnaires again at three and six months after initial assessment and so these participants will be in the study for about six months. **Those taking part in the QST will be in the study for additional hour.**

Participant Withdrawal

Participants will be informed through the information sheet and consent form that they can withdraw from the study at any given point without providing a reason

and without consequence. If consent is withdraw, they will be immediately withdrawn from the study. However, participants' data cannot be erased and they will be made aware that data collected so far may still be used in the analysis. There will be an attempt to replace withdrawn participants in the study.

Informed consent

The participants in Study 1 will only need to sign their consent form if they are interested in taking part in future research – completion of the questionnaires will be taken as implied consent. In contrast, all participants in the sub-study of Study 1 and Study 2 will provide written informed consent. In Study 1 (when applicable), the sub-study and Study 2 the consent form will be signed and dated by the participant and researcher obtaining consent for the study. Prior to obtaining consent, the participants will have been sent an information sheet explaining the purpose, nature and methods of the study as well as the risks, burdens and potential benefits. It will be made clear to participants that participation is voluntary and they can withdraw from the study at any point without providing a reason and without consequence. All participants will be provided with a contact number so that they can ask the researchers about the study. Three copies of the consent form will be made, one for the participant to keep for their reference, one for the study file, and one for their medical record. Should there be any subsequent amendment to the final protocol, which might affect participation in the study, continuing consent will be obtained using an amended consent form which will be signed and dated by the participant.

STATISTICS

Methods

The data from Study 1 will be analysed separately from Study 2 using a variety of different methods. We intend to use Rasch Analysis to refine the questionnaires and remove poorly performing items. The Rasch model assumes that questionnaire responses are a probabilistic function of two variables: (1) the person providing the response and (2) the difficultly of the item (Wright & Panchapakesan, 1969). By testing the fit between the model and data one can draw conclusions over whether specific items can be legitimately summed to characterise a person. Indeed the analysis allows researchers to identify questionnaire items that particularly deviate from the model's prediction. This information will be used to refine existing questionnaires. Internal consistency will be reported as the Person Separation Index, which is calculated from the Rasch Model, and Factor Analysis will be used to identify discrete dimensions.

Data from the QST sub-study will be analysed separately from Study 1, but before the start of Study 2. Pain pressure thresholds (mean, standard deviation, and 95% confidence intervals) will be reported in units of pressure (kg/cm^2) and summarised for each anatomical site using descriptive statistics. Differences between sites will be evaluated. Inter- and intra-individual and intra-examiner reliability of pain pressure threshold measurements will be reported as repeatability coefficients

(intraclass correlation coefficients) for each anatomical site. Acceptability of the procedure to participants will be reported descriptively. The analysis of the sub-study QST data will inform future analyses planned in Study 2.

The questionnaire data from Study 2 will be analysed using the same methods as Study 1 to confirm the factor structure of the questionnaires. **In addition, test-retest reliability will be assessed using the three and six month follow-up data. Specifically, Kappa Coefficients for individual items and Bland and Altman Plots or Intraclass correlations for total scores. Multiple regression will also be conducted to assess potential mediators and moderators between pain and quality of life. Finally, a Delphi process will be used to identify mechanistic item groupings. To achieve this, we will ask a multidisciplinary group of experts in OA and pain, including clinical and non-clinical scientists, to identify possible item groupings within the refined questionnaire set. These item groupings will be iteratively refined until the group reach consensus. The results of this analysis will then be compared to that produced by the Rasch Analysis. The experts used in the Delphi process will be blind to the quantitative analysis. The QST data from Study 2 will be analysed using the same methods as the sub-study. Pain Pressure Thresholds will be reported and differences between sites will be evaluated. These findings will be compared to the questionnaire data.**

SAMPLE SIZE AND JUSTIFICATION

Sample size calculations were based on the Rasch Analysis, because this is the primary form of data analysis in Study 1 and Study 2. There are no clear guidelines on sample size for Rasch Analysis, but in general larger sample sizes provide more stable item calibrations. Linacre (1994) suggests that a sample size of 250 participants would provide a high degree of confidence (99% and above) that the item calibrations are stable (i.e., at least within 0.5 logit). Note that this sample size would also be more than sufficient for the multiple regression analysis planned for Study 2. For example, only 145 participants would be required to have 90% power (α = 0.05) to test a multiple regression model with 10 predictor variables and a moderate effect size (e.g., f^2 = 0.15 – Cohen, 1988). Thus we decided to recruit 250 participants in Study 1 and Study 2 (total n = 500). It is important to mention that we plan to send out 500 invitations in study 1, because we expect a response rate of approximately 50%. **We will place no limits on the number of invitations sent out in Study 2 because it is difficult to predict the response rate from such varied recruitment sources. However, recruitment will be staggered to ensure that we do not send out too many invitations.** Any additional participants (i.e., more than 250 participants in Study 1 or Study 2) will be included in the analysis.

ADVERSE EVENTS

The occurrence of adverse events as a result of participation within this study is not expected and no adverse event data will be collected. However, if any unexpected adverse events occur, the chief investigator and regulatory authorities will be notified and the incident will be appropriately investigated and acted upon.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The study will not be initiated before the protocol, consent forms and participant information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), and the respective NHS Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice (GCP), and the Department of Health Research Governance Framework for Health and Social Care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining informed consent will be in accordance with the REC guidance, and GCP and any other regulatory requirements that might be introduced. The participant and researcher obtaining consent will sign and date the consent form (when applicable – see above). Three copies of the form will be made, one for the participant to keep for their reference, one for the study file and one for their medical records. The decision regarding participation in the study is entirely voluntary. The investigator will emphasize to participants that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No study-specific interventions will be done before informed consent has been obtained. The investigator will inform the participant of any relevant information that becomes availsble during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable, they will be asked to sign revised consent forms. If the consent form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended consent form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Case Report Forms

Each participant will be assigned an identity code, which will be used on all recordings (i.e., documents and electronic database). The identity code will be composed of the participants' initials (of first and last names separated by either a hyphen or a middle name initial when available), date of birth (dd/mm/yy) and a study number. The questionnaires will be assigned a study number before being sent out to potential participants. An independent confidential record of the participant's name, date of birth, address, local hospital number or NHS number, and a study number, will be kept to permit identification of all participants in case additional follow-up is required.

Source documents

Source documents include consent forms and questionnaire response sheets. All materials will be safely stored, at the Institute of Work, Health and Organisations, at the University of Nottingham in locked cabinets. Only authorised individuals will have access to study documentation. Electronic data will be stored on password protected computers at the University of Nottingham and storage devices (e.g., CD). Data entry and analysis will occur at the **University of Nottingham.**

Direct access to source data / documents

The Case Report Forms (CRF) and all source documents shall be made available at all times for review by the chief investigator, Sponsor's designee and inspection by relevant regulatory authorities.

DATA PROTECTION

All study staff and investigators will endeavour to protect the rights of the participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. All source documents will be held securely, in locked cabinets on university premises. Access to the information will be limited to members of the research team. Electronic data will be stored on password protected computers at the University of Nottingham and storage devices (e.g., CDs). All data will also be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method). Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for clinical study participants and study staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but study participants may have recourse through the NHS complaints procedures. The University of Nottingham has taken out an insurance policy to

provide indemnity in the event of a successful litigious claim for proven non-negligent harm.

STUDY CONDUCT

Study conduct will be subject to systems audit for inclusion of essential documents; permissions to conduct the study; CVs of study staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria and timeliness of visits); accountability of study materials and equipment calibration logs.

STUDY DATA

Monitoring of study data will include confirmation of informed consent; source data verification; data storage and data transfer procedures back-up and disaster recovery of any local databases and validation of data manipulation. The Study Coordinator, or where required, a nominated designee of the Sponsor, will carry out monitoring of study data as an ongoing activity. Study data and evidence of monitoring and systems audits will be made available for inspection by the REC as required.

RECORD RETENTION AND ARCHIVING

In compliance with the International Conference on Harmonisation (ICH) / GCP guidelines and in accordance with the University of Nottingham Research Code of Conduct, the chief investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least seven years or for longer if required. If the chief investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility. The study documents held by the chief investigator on behalf of the Sponsor will be finally archived at secure archive facilities at the University of Nottingham. This archive will include all study databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this study at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical or personal information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification codes. Data generated as a result of this study will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

The findings of the study will be disseminated by seeking publication in peer-reviewed journals and presented in conferences.

USER AND PUBLIC INVOLVEMENT

There has been no direct user involvement in this study apart from the selection of the research for funding by Arthritis Research UK. This study is part of a programme of research by the Arthritis Research UK Pain Centre and service users will be involved in reviewing the studies completed by the centre.

STUDY FINANCES

The study is funded by Arthritis Research UK.

Participant stipends and payments

Participants will not be paid to participate in the study. Any expenses for attending hospital clinics for the purpose of research will be reimbursed.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name) _____

Signature: _____

Date: _____

Co- investigator: (name) _____

Signature: _____

Date: _____

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Appendix 8

Institute of Work, Health & Organisations
http://www.nottingham.ac.uk/iwho

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Bryan Moreton

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08/07/2013

Dear Bryan

I-WHO Ethics Committee Review

Thank you for submitting your proposal on "A test of interrater reliability for establishing pain pressure thresholds with quantitative". This proposal has now been reviewed by I-WHO's Ethics Committee to the extent that it is described in your submission.

I am happy to tell you that the Committee has found no problems with your proposal. If there are any significant changes or developments in the methods, treatment of data or debriefing of participants, then you are obliged to seek further ethical approval for these changes.

We would remind all researchers of their ethical responsibilities to research participants. The Codes of Practice setting out these responsibilities have been published by the British Psychological Society. If you have any concerns whatsoever during the conduct of your research then you should consult those Codes of Practice and contact the Ethics Committee.

You should also take note of issues relating to safety. Some information can be found in the Safety Office pages of the University web site. Particularly relevant may be:

The *Safety Handbook*, which deal with working away from the University.
http://www.nottingham.ac.uk/safety/
Safety circulars: Fieldwork P5/99A on http://www.nottingham.ac.uk/safety/fieldwork.htm
Overseas travel/work P4/97A on http://www.nottingham.ac.uk/safety/overseas.htm
Risk assessment on http://www.nottingham.ac.uk/safety/risk-assessment.htm

Responsibility for compliance with the University Data Protection Policy and Guidance lies with all researchers.

Ethics Committee approval does not alter, replace or remove those responsibilities, nor does it certify that they have been met.

We would remind all researchers of their responsibilities:

- to provide feedback to participants and participant organisations whenever appropriate, and
- to publish research for which ethical approval is given in appropriate academic and professional journals.

Yours sincerely

Nadina Lincoln

Professor Nadina Lincoln
Chair IWHO Ethics Committee

Appendix 9

Protocol version 1.0 (30.06.2013)

Title	A test of interrater reliability for establishing pain pressure thresholds with quantitative sensory testing.
Short title	Interrater reliability in QST
Chief Investigator	Dr Bryan Moreton Institute of Work, Health and Organisations Jubilee Campus Wollaton Road Nottingham NG8 1BB
Co-Investigators	Miss Victoria Tew Trainee Clinical Psychologist Trent Doctorate in Clinical Psychology, University of Nottingham Institute of Work, Health and Organisations Jubilee Campus Wollaton Road Nottingham NG8 1BB Mrs Maggie Wheeler Clinical co-ordinator (Research) Arthritis Research UK Pain Centre Academic Rheumatology Clinical Sciences Building City Hospital NG5 1PB
Objectives	To examine the interrater reliability of Pain Pressure Thresholds (PPT) using Quantitative Sensory Testing (QST).
Study Configuration	Single centre study.
Sample size estimate	The sample size estimate was based on intraclass correlation coefficients (ICC). The value of *n* was fixed to two (i.e., two raters). The sample size calculation (based on Walter et al., 1998) was designed to test for an ICC of 0.9 and the null value set at 0.7 (cf., Chesterton et al., 2007). With an alpha of 0.05 and a beta of 0.20, 19 participants would be needed.
Number of participants	Approximately 20 participants.
Eligibility criteria	Participants will be eligible if: • They are able to take part in the procedure.

	• They do not have any significant medical or psychiatric conditions that could adversely affect the results. • They are capable of providing informed consent.
Description of procedure	The study will be carried out in accordance with previous QST studies conducted at the Arthritis Research UK Pain Centre (University of Nottingham). Participants will be recruited opportunistically. They will be provided with an information sheet and asked to sign and date a consent form before starting the study. Those indicating an interest in taking part will first be screened by a researcher to ensure eligibility and to confirm that they have understood the contents of the information sheet. Participants will be invited to take part in QST at Academic Radiology or Academic Rheumatology (University of Nottingham), in an assessment room. Before starting the procedure, the participants will be asked to complete a few questions about their current pain status (e.g., a Numeric Rating Scale 0-10 for any pain in any region of the body). PPT will be assessed using an electronic algometer with a laptop recording/display device. The algometer as a 1cm diameter probe, which will be applied with graded pressure to test sites. At the time at which the participant indicates that the stimulus is experienced as pain rather than pressure, the probe will be retracted immediately ceasing stimulation. The participants will be familiarised with the procedure before the start of the assessment by applying the stimulus to a learning site on one hand. This will ensure that the participant understands the nature of the stimulus and how to respond when pain is felt. The stimulus will be applied to sites on the knee (medial joint line and lateral joint line), lower leg (tibialus anterior) and sternum. These sites were chosen on the basis of systematic review of pressure algometry studies. The stimulus will be applied to each test site three times with rest intervals between. Two minute rest intervals will be interspersed between sites. The participants will be tested once by one researcher (V.T. or M.W.) at each body site, then, following a short five minute break, they will be tested by a second researcher. This means that the participants will go through the entire test procedure twice. This design was chosen to protect against wide-up effects. The rest periods will protect against any fatigue caused by repetitive testing. The order of researchers will be counter-balanced so that half of the participants are tested first by V.T. and the other half by M.W. to control for order effects. The researchers will have undergone specialist training with a Somedic Sensebox algometer. In addition, the participants will be able to stop the testing procedure at any

	time and can withdraw their consent without giving an explanation. All data collected during the study will be stored anonymously and in accordance with the data protection act (1998). Dr Bryan Moreton will be custodian of the data.
Duration of study	The study will run approximately 6 to 8 weeks in total. The testing procedure will take approximately one hour per participant.
Outcome measures	The primary outcome will be PPT.
Statistical methods	The data will be summarised for each anatomical site using the mean and standard deviation. In addition, 95% confidence intervals will be calculated. Interrater reliability will be calculated using intraclass correlation coefficients.

Appendix 10

The University of Nottingham

A test of interrater reliability for establishing pain pressure thresholds with quantitative sensory testing.

Chief Investigator: Dr Bryan Moreton
Co-investigators: Miss Victoria Tew and Mrs Maggie Wheeler

INFORMATION SHEET (version 1, 30.06.2013)

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the University of Nottingham is doing the research, how your information will be used, what the study will involve and the potential benefits and risks. Take your time to read the following information and feel free to talk to others about the study if you wish. Please, ask us if there is anything that is not clear.

WHY IS THIS STUDY BEING DONE?
Quantitative Sensory Testing (QST) is a method used to establish pain thresholds that can be contrasted between different body areas and across different individuals. This study is being conducted to examine how reliable QST measurements are when administered by different people (interrater reliability).

WHY HAVE I BEEN INVITED?
You have been invited because you may be able to help us in our research study.

DO I NEED TO TAKE PART?
NO IT IS ENTIRELY VOLUNTARY.
It is up to you to decide whether to join the study. You do not have to be involved in this research if you do not want to. If you decide that you do not want to take part, you do not have to give a reason for this. If you agree to take part, we will ask you to complete a sign a consent form.

WHAT ARE WE ASKING YOU TO DO?
QST is a non-invasive test (i.e., no needles are used) that measures how sensitive nerves are by recording the smallest pressure change that is required to be felt as pain. If you choose to take part, you will be invited to answer some questions about your current state of pain and to carry out QST at Academic Rheumatology or Academic Radiology (University of Nottingham).

If you participate, during the test, the researcher will press a blunt probe onto certain parts of your body to apply pressure. The pressure probe consists of a rod with an end the size of a 5p piece, mounted in a hand held device connected to a computer. The probe will be lightly pressed onto your skin then the force with which the probe is pressed onto your skin will be gradually increased. As soon as you indicate that the pressure is felt as pain, the researcher will immediately take the probe off your skin. The sensation of pain will be mild and temporary in nature. The pressures used have been selected to not damage your skin.

The researcher may put the probe on your knees, legs, and the front of your chest. Each region will be tested three times with short rest periods between. You will be tested at each site once by one researcher, then following a short five minute break, you will be tested again by a second researcher so that their measurements can be compared. Before starting the procedure, we will familiarise you with the test by

applying the probe to one of your hands so that you will know what to expect and how to respond as soon as you feel any pain. You will be able to indicate at any point if you do not wish to continue.

EXPENSES AND PAYMENTS
All travel expenses will be fully reimbursed for attending the test. There will however be no payment for taking part in the study.

WHAT ARE THE BENEFITS OF TAKING PART?
Taking part in our study means that you may possibly help people with pain in the future, as the information may be used to refine the way we assess pain thresholds. We do not expect you to directly gain from taking part.

WHAT ARE THE POSSIBLE DISADVANTAGES OF TAKING PART?
We appreciate that taking part will use your time and may therefore be inconvenient. You will feel slight discomfort in the area where the QST probe is placed. However, the feeling will be temporary and any aspect of your involvement in the study can stop at any time if you do not wish to continue.

WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. Information will not be used or disclosed in a form that might identify you without your consent.

WHAT WILL HAPPEN IF I DON'T WANT TO CARRY ON WITH THE STUDY?
Your participation is voluntary and you are free to withdraw at any time, without giving any reason by either informing the researcher administering the QST or phoning the study contacts on either 0115 846 6545 or 0115 823 1676. If you withdraw then the information collected so far cannot be erased and this information may still be used in the project analysis.

WHAT WOULD WE DO WITH THE INFORMATION THAT YOU GIVE US?
The QST data will be transferred to an electronic database and used in analysis. The electronic files will be stored on password protected computers and storage devices (e.g., CDs). Any research information on paper will be stored at the University of Nottingham in locked cabinets for seven years before being destroyed. Personal information will be stored separately from research data and we will assign an anonymous identity code to all data. Only the researchers and the authorised representatives of the University of Nottingham will have access to your personal data. Your personal details will not be provided to anyone else, or used for any purpose other than our research. They will be destroyed after it is no longer necessary to contact you.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?
The results of the study may be presented to other researchers, at meetings and through publication in scientific journals.

If you ask the researcher, we would be happy to send you a copy of the results when they are available.

WHO HAS REVIEWED THE STUDY?
The research has been looked at by an independent group of people, called a Research Ethics Committee, to protest your interests.

WHAT IF THERE IS A PROBLEM?
If you have concerns about any aspect of the way you have been treated during the course of the study, please discuss them with the researcher administering the QST or the Chief Investigator.

FUTURE CONTACT
We would be grateful if you could indicate on the consent form whether you would be willing for us to contact you about any further parts of our research in the future. **Please note that the boxes on the consent form need to be initialled rather than ticked. It is important that you sign and date the consent form and initial rather than tick the boxes.**

If you have any further questions about this study, please contact either:

Dr Bryan Moreton (Chief Investigator)
University of Nottingham
Institute of Work, Health and Organisations
International House
Jubilee Campus
Wollaton Road
Nottingham, NG8 1BB
Telephone: 0115 846 6545
Email: bryan.moreton@nottingham.ac.uk

Mrs Maggie Wheeler
Academic Rheumatology
Clinical Sciences Building
City Hospital
Hucknall Road
Nottingham
NG5 1PB
Telephone: 0115 823 1676
Email: maggie.wheeler@nottingham.ac.uk

Thank you for taking the time to read this invitation.

Appendix 11

The University of Nottingham

CONSENT FORM
(Version 1
30.06.2013)

A test of interrater reliability for establishing pain pressure thresholds with quantitative sensory testing.

Chief Investigator: Dr Bryan Moreton
Co-investigators: Miss Victoria Tew and Mrs Maggie Wheeler

Please initial box

1. I confirm that I have read and understand the information sheet version number **1** dated **30.06.2013** for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐

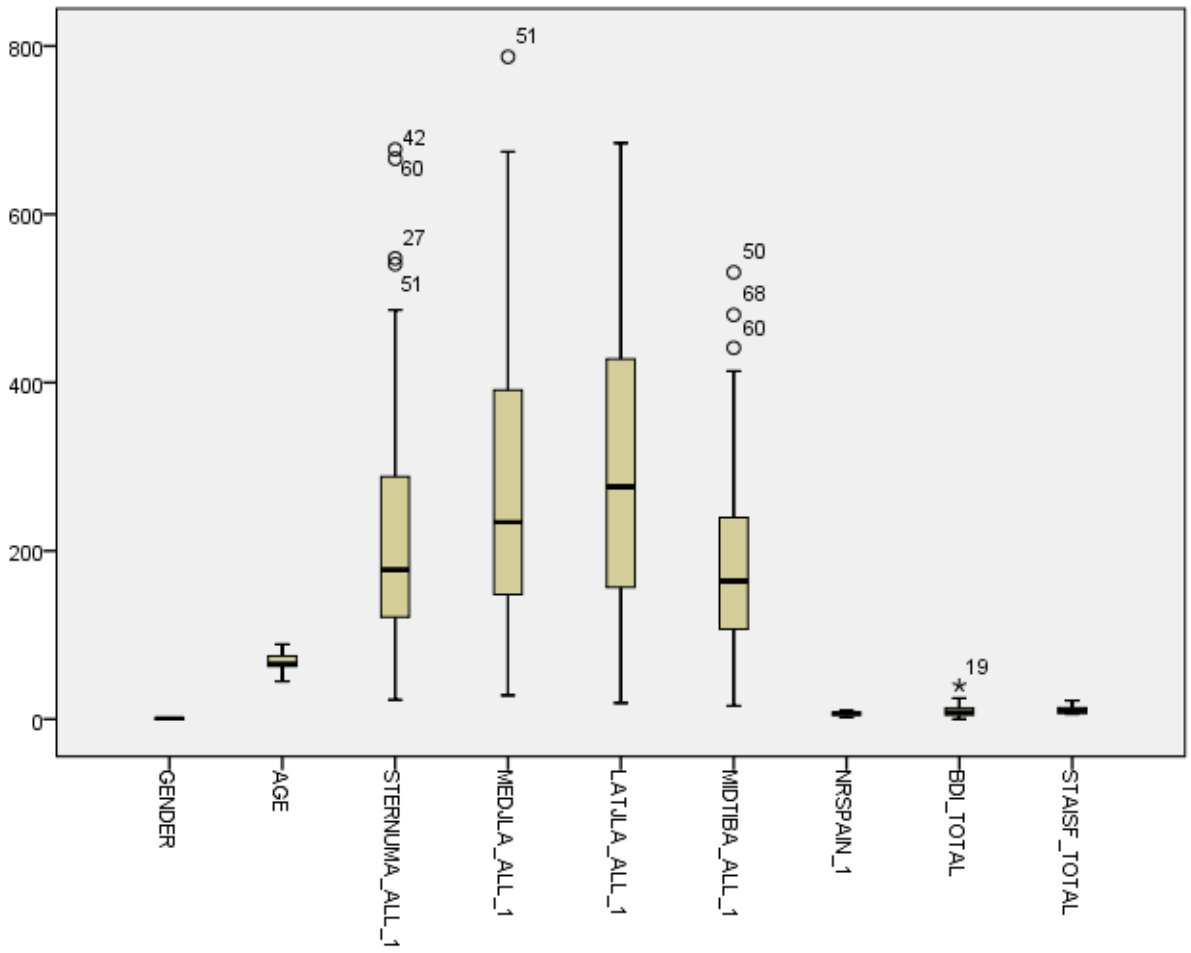
3. I understand that relevant sections of my data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐

4. I agree to take part in the above study. ☐

5. (Optional) I agree to being contacted in the future about other research studies. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix 12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400
200
0
51
42
60
27
51
50
68
60
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GENDER
AGE
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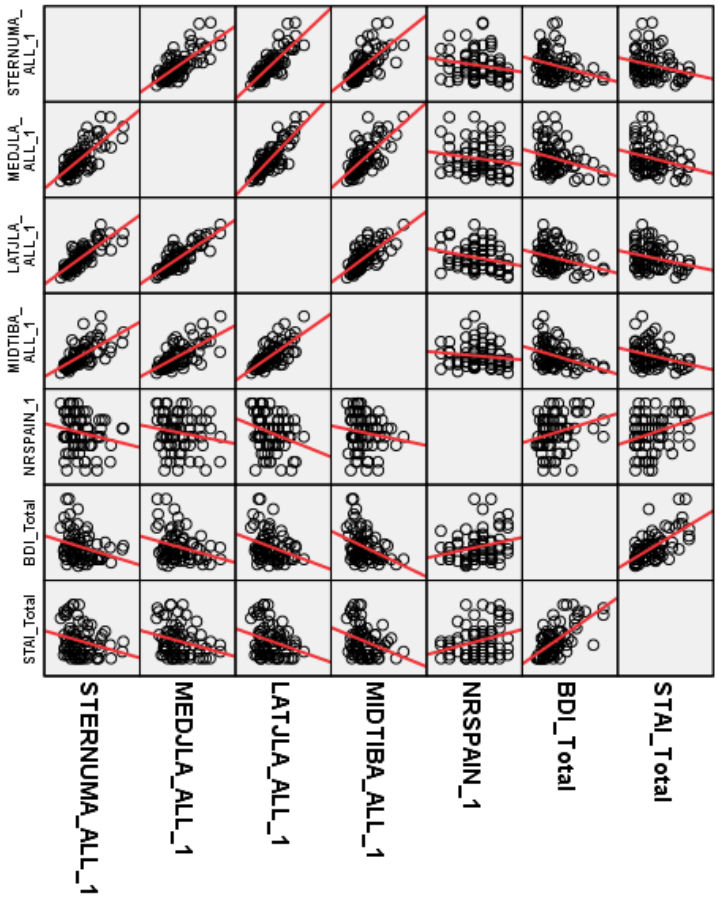
MEDJLA_ALL_1
LATJLA_ALL_1
MIDTIBA_ALL_1
NRSPAIN_1
BDI_TOTAL
STAISF_TOTAL

Appendix 13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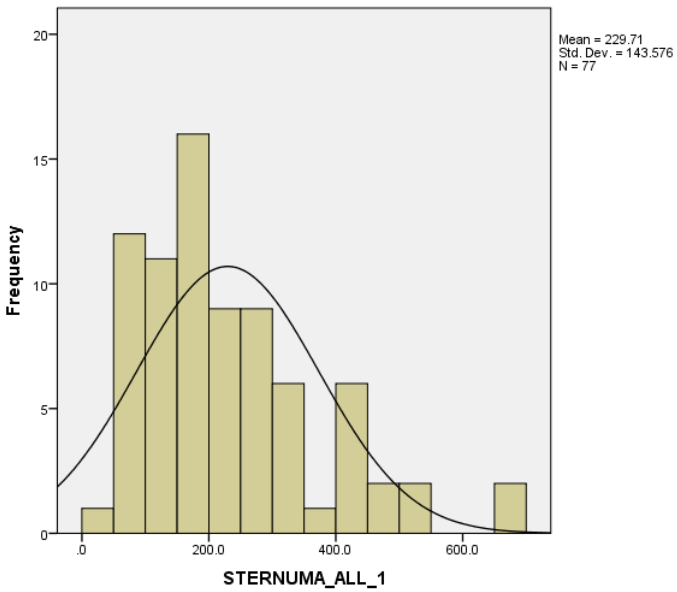
NRSPAIN_1
BDI_Total
STAI_Total

Appendix 14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Std. Dev. = 143.576
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Frequency
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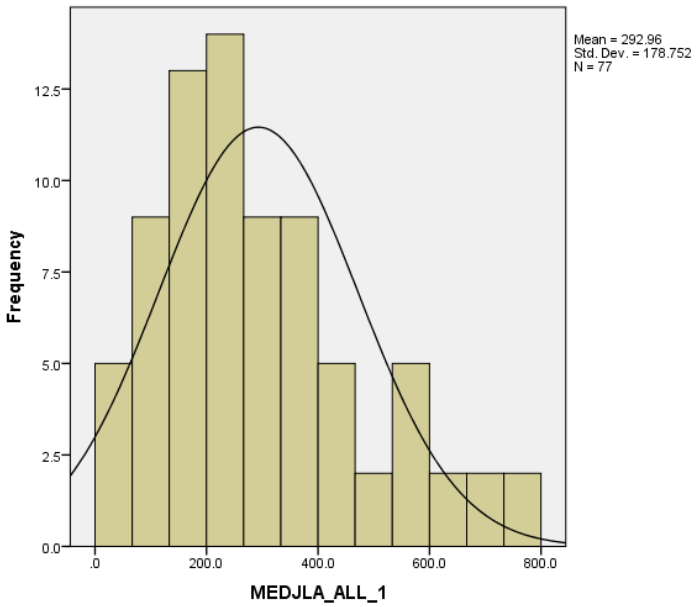
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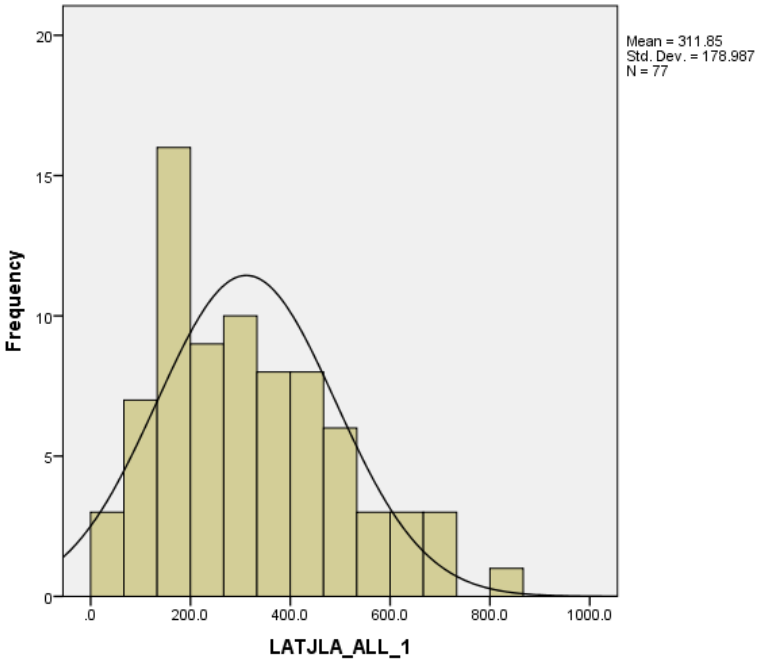
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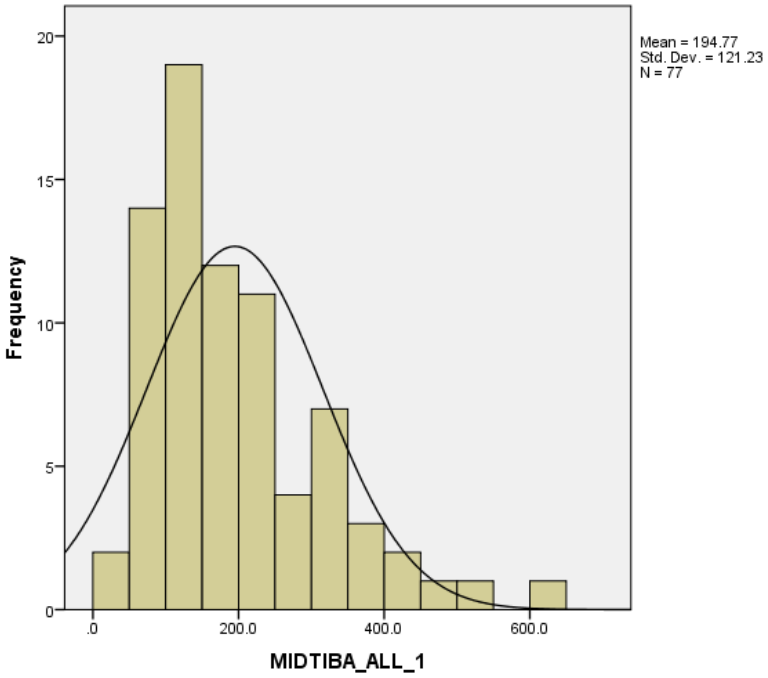
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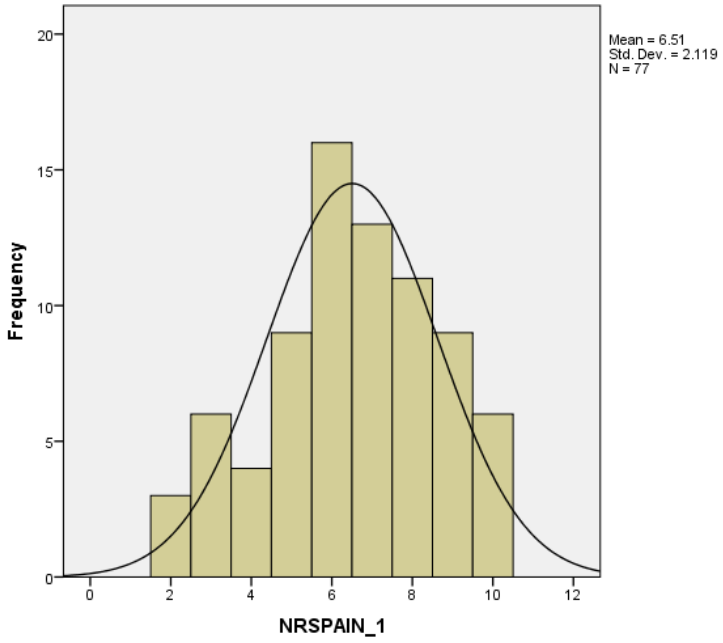
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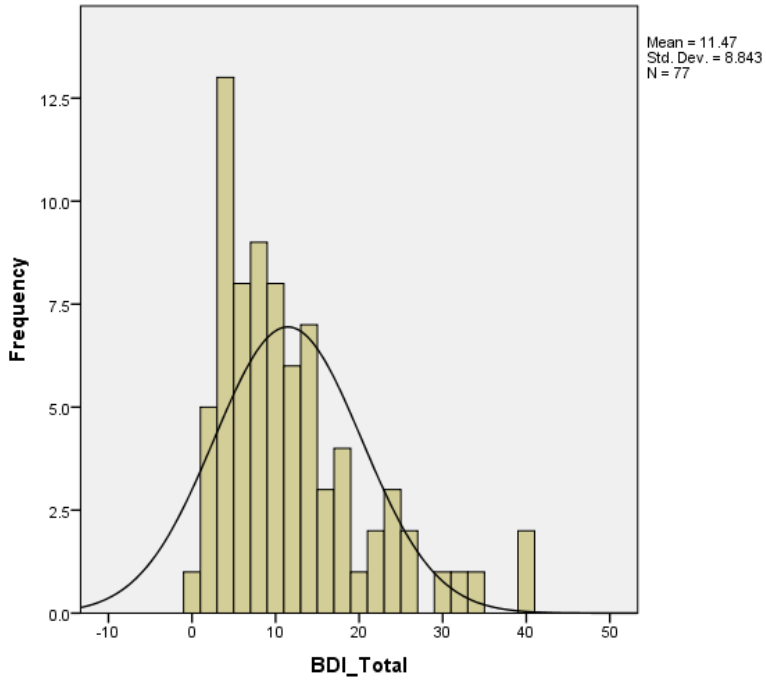
Std. Dev. = 2.119
N = 77
Frequency
NRSPAIN_1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Frequency
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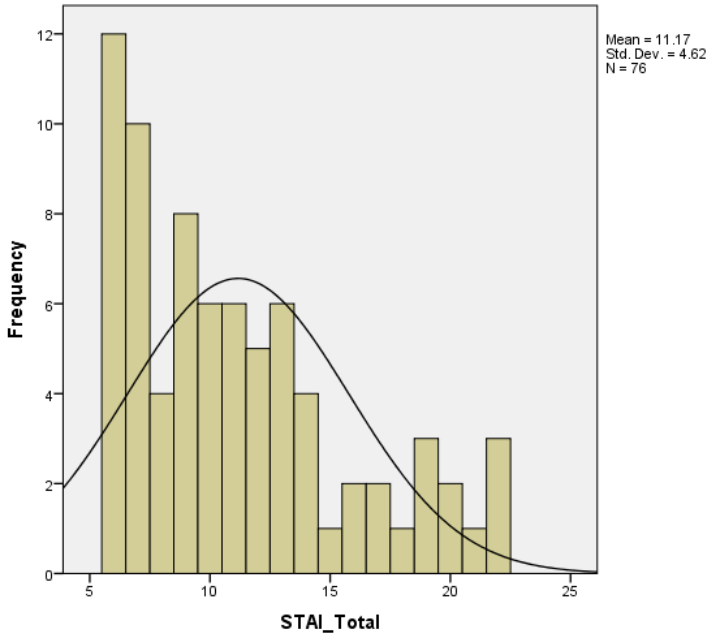
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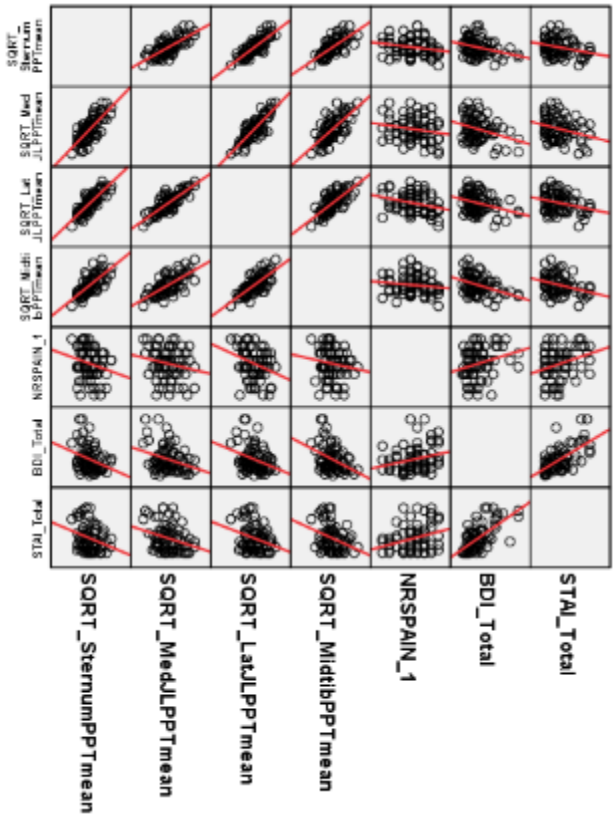
Frequency
STAI_Total

Appendix 15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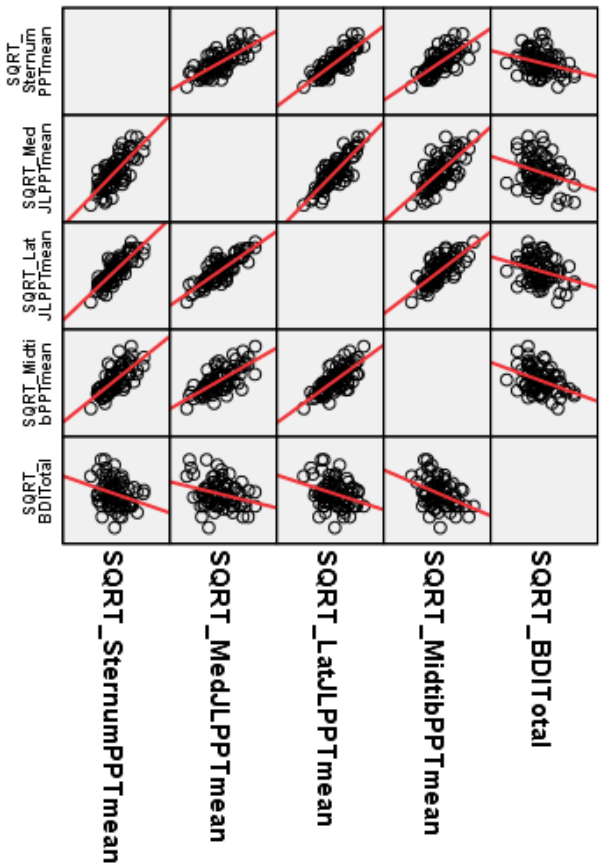
NRSPAIN_1
BDI_Total
STAI_Total

Appendix 16


SQRT_ BDITotal
SQRT_ MidtibPPTmean
SQRT_Lat JLPPTmean
SQRT_Med JLPPTmean
SQRT_ SternumPPTmean
SQRT_SternumPPTmean
SQRT_MedJLPPTmean
SQRT_LatJLPPTmean
SQRT_MidtibPPTmean
SQRT_BDITotal

Appendix 17

Mann-Whitney analysis SPSS output for each factor

Ranks

	GENDER	N	Mean Rank	Sum of Ranks
SQRT_SternumPPTmean	M	34	45.21	1537.00
	F	43	34.09	1466.00
	Total	77		

Test Statistics[a]

	SQRT_SternumPPTmean
Mann-Whitney U	520.000
Wilcoxon W	1466.000
Z	-2.164
Asymp. Sig. (2-tailed)	.030

a. Grouping Variable: GENDER

Ranks

	GENDER	N	Mean Rank	Sum of Ranks
SQRT_MedJLPPTmean	M	34	46.76	1590.00
	F	43	32.86	1413.00
	Total	77		

Test Statistics[a]

	SQRT_MedJLPPTmean
Mann-Whitney U	467.000
Wilcoxon W	1413.000
Z	-2.708
Asymp. Sig. (2-tailed)	.007

a. Grouping Variable: GENDER

Ranks

	GENDER	N	Mean Rank	Sum of Ranks
SQRT_LatJLPPTmean	M	34	45.59	1550.00
	F	43	33.79	1453.00
	Total	77		

Test Statistics[a]

	SQRT_LatJLPPTmean
Mann-Whitney U	507.000
Wilcoxon W	1453.000
Z	-2.298
Asymp. Sig. (2-tailed)	.022

a. Grouping Variable: GENDER

Ranks

	GENDER	N	Mean Rank	Sum of Ranks
SQRT_MidtibPPTmean	M	34	45.62	1551.00
	F	43	33.77	1452.00
	Total	77		

Test Statistics[a]

	SQRT_MidtibPPTmean
Mann-Whitney U	506.000
Wilcoxon W	1452.000
Z	-2.308
Asymp. Sig. (2-tailed)	.021

a. Grouping Variable: GENDER

Ranks

	GENDER	N	Mean Rank	Sum of Ranks
NRSPAIN_1	M	34	38.91	1323.00
	F	43	39.07	1680.00
	Total	77		

Test Statistics[a]

	NRSPAIN_1
Mann-Whitney U	728.000
Wilcoxon W	1323.000
Z	-.031
Asymp. Sig. (2-tailed)	.975

a. Grouping Variable: GENDER

Ranks

	GENDER	N	Mean Rank	Sum of Ranks
SQRT_BDITotal	M	34	35.04	1191.50
	F	43	42.13	1811.50
	Total	77		

Test Statistics[a]

	SQRT_BDITotal
Mann-Whitney U	596.500
Wilcoxon W	1191.500
Z	-1.383
Asymp. Sig. (2-tailed)	.167

a. Grouping Variable: GENDER

Ranks

	GENDER	N	Mean Rank	Sum of Ranks
STAI_Total	M	34	39.84	1354.50
	F	42	37.42	1571.50
	Total	76		

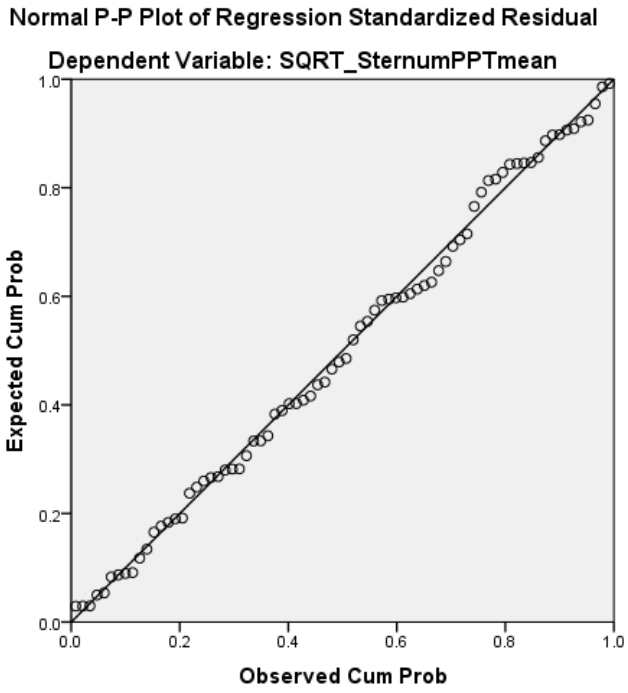
Test Statistics[a]

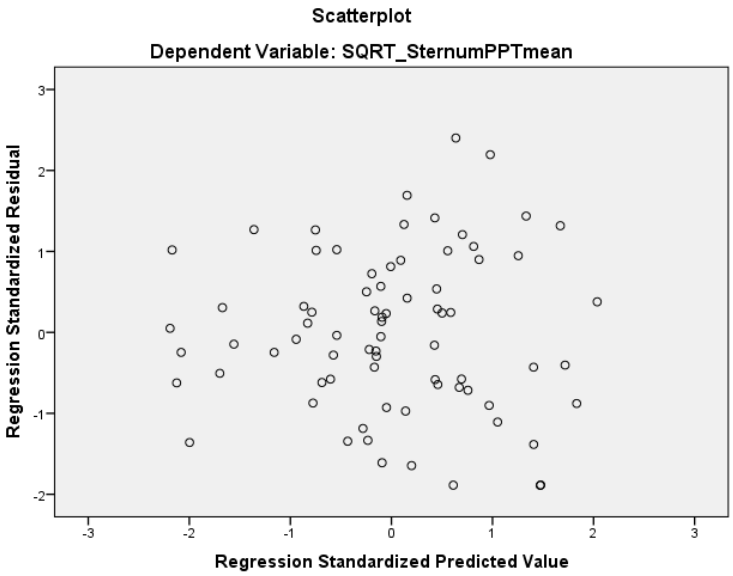
	STAI_Total
Mann-Whitney U	668.500
Wilcoxon W	1571.500
Z	-.478
Asymp. Sig. (2-tailed)	.633

a. Grouping Variable: GENDER

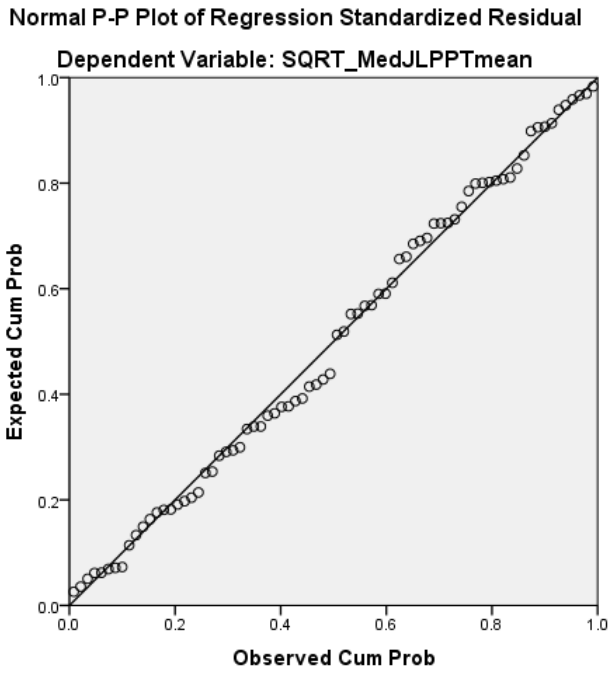
Appendix 18

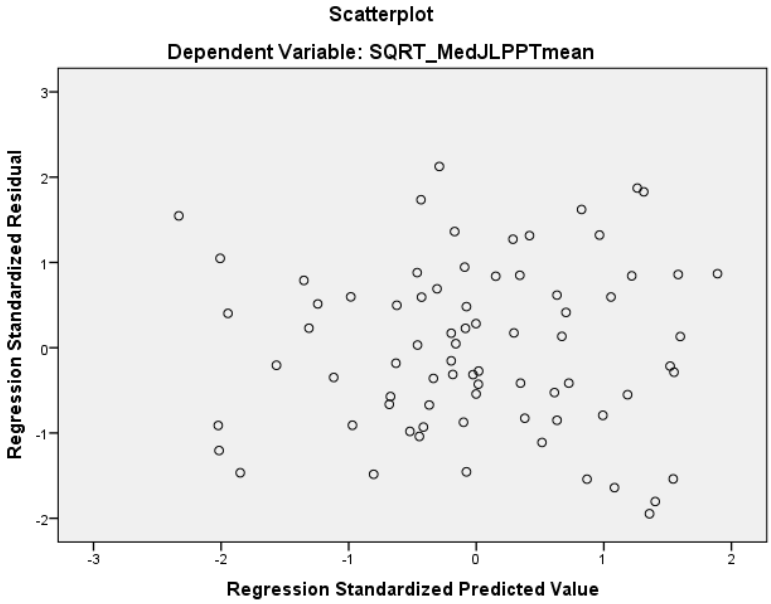
Sternum PPT:



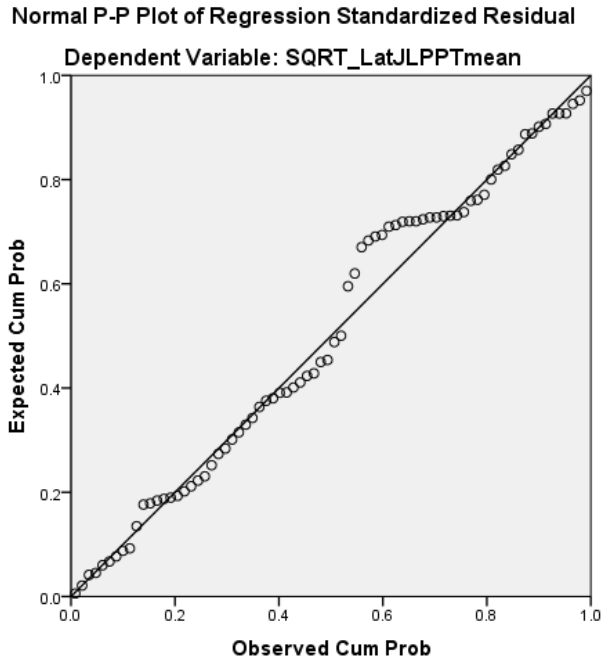


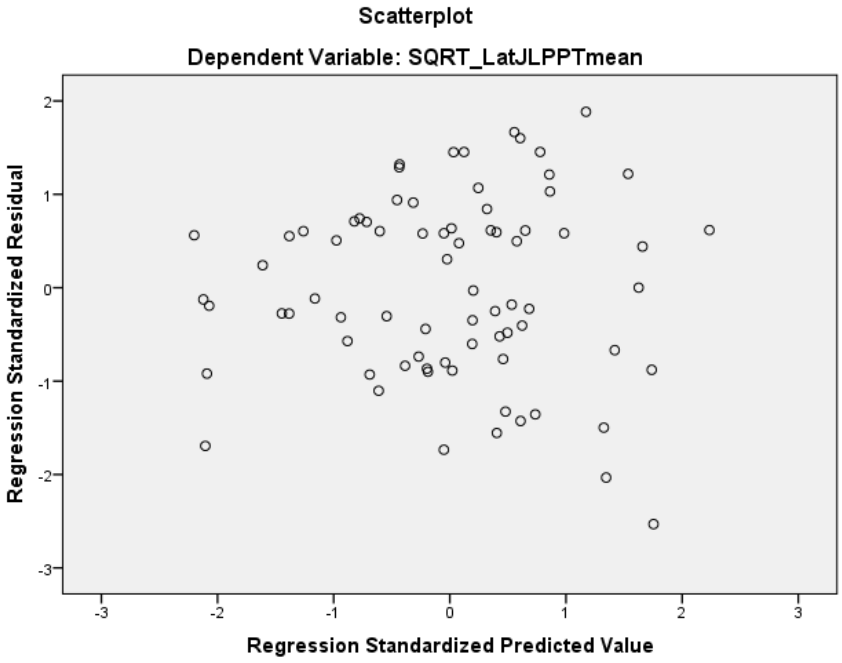
Medial knee joint-line PPT:



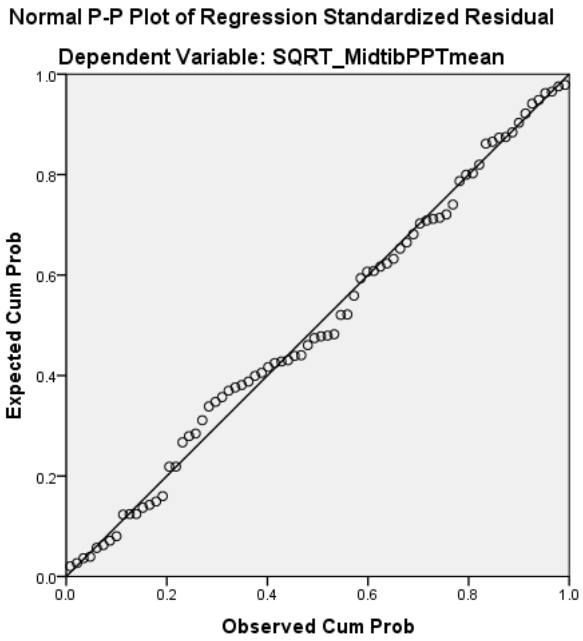


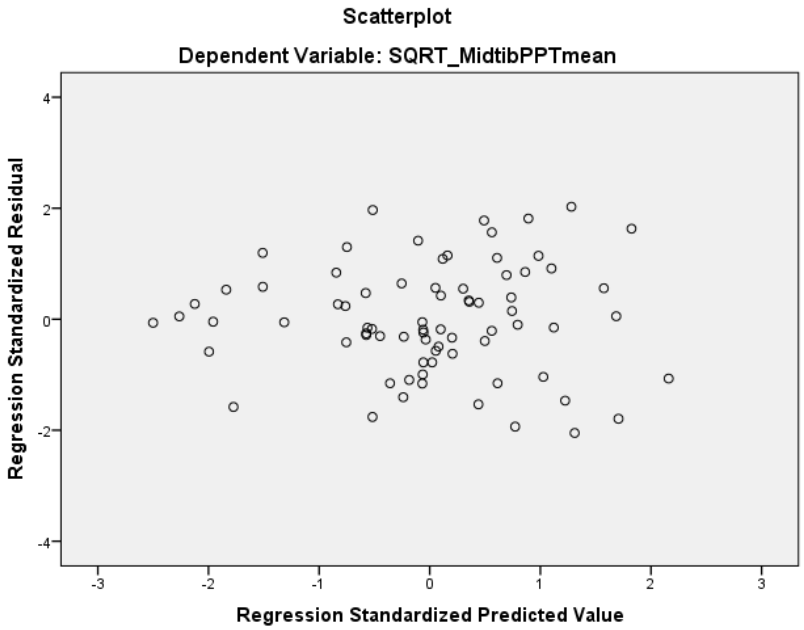
Lateral knee joint-line PPT:





Medial tibia mid-shaft PPT:





Appendix 19

2 Class Intervals

	Class Interval:	
STAI-SF item	**1**	**2**
1	107	100
2	106	101
3	107	99
4	107	100
5	107	101
6	107	101
Mean frequency:	***106.8***	***100.3***
Ideal value:	*50*	*50*

3 Class Intervals

	Class Interval:		
STAI-SF item	**1**	**2**	**3**
1	64	70	73
2	63	70	74
3	64	70	72
4	64	69	74
5	64	70	74
6	64	70	74
Mean frequency:	***63.8***	***69.8***	***73.5***
Ideal value:	*50*	*50*	*50*

4 Class Intervals

	Class Intervals:			
STAI-SF item	**1**	**2**	**3**	**4**
1	63	59	49	36
2	63	58	49	37
3	63	59	57	27
4	63	58	49	37
5	63	59	49	37
6	63	59	49	37
Mean frequency:	***63.0***	***58.7***	***50.3***	***35.2***
Ideal value:	*50*	*50*	*50*	*50*

5 Class Intervals

	Class Interval:				
STAI-SF item	**1**	**2**	**3**	**4**	**5**
1	41	47	46	37	36
2	41	46	46	37	37
3	41	47	46	45	27
4	41	47	45	37	37
5	41	47	46	47	27
6	41	47	46	47	27
Mean frequency:	***41.0***	***46.8***	***45.8***	***41.7***	***31.8***
Ideal value:	*50*	50	*50*	*50*	*50*

6 Class Intervals

	Class Interval:					
STAI-SF item	**1**	**2**	**3**	**4**	**5**	**6**
1	41	23	43	39	35	26
2	41	46	34	38	37	11
3	41	23	43	39	33	27
4	41	23	43	38	35	27
5	41	47	34	38	37	11
6	41	47	34	38	37	11
Mean frequency:	***41.0***	***34.8***	***38.5***	***38.3***	***35.7***	***18.8***
Ideal value:	*50*	50	*50*	*50*	*50*	*50*

Appendix 20

	Class Intervals:			
STAI-SF item	**1**	**2**	**3**	**4**
1	42	49	59	57
2	42	48	59	58
3	42	49	59	56
4	42	49	58	58
5	42	49	59	58
6	42	49	59	58
Mean frequency:	***42.0***	***48.8***	***58.8***	***57.5***
Ideal value:	*50*	*50*	*50*	*50*