Somatic and psychological predictors of response to intra-articular corticosteroid injection in knee osteoarthritis

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Background: Intra-articular corticosteroid injections (IACI) are a commonly used treatment for painful knee osteoarthritis (OA). Response to treatment varies the reason for which is unclear. Further there are no data concerning the impact of accuracy of injection and psychological factors including illness perceptions, pain catastrophizing and depression on outcome following IACI.

Objectives: i) to undertake a systematic review looking at predictors of response to IACI in patients with symptomatic knee OA and, ii) to determine the role of psychological factors and accuracy of injection in predicting response to IACI.

Methods: A systematic review was conducted using electronic databases for randomised trials and observational studies looking at predictors of response to IACI in knee and hip OA. An observational study of 141 consenting patients (105 primary OA and 36 secondary OA in the context of well controlled rheumatoid arthritis) receiving routine IACI as part of clinical care for knee OA was conducted including baseline assessment and outcome assessments at 3 and 9 weeks. Response was defined as at least 40% reduction of pain from baseline, using the Western Ontario and McMaster Universities Arthritis Index (WOMAC). Assessment included ultrasound (US) for features of synovial inflammation), radiographs, and assessment of psychological factors including the revised illness perception questionnaire (IPQR). Accuracy of injection was assessed using US. Characteristics of responders and non-responders to IACI at 3 and 9 weeks were determined using univariate statistics and significant factors entered into logistic regression models.

Results: The systematic review found no consistent evidence for any disease or non-disease related predictor of response and no systematic exploration of the effects of psychological factors or accuracy of injection on treatment response. In the observational study, 83 (53%) of 141 subjects were responders to IACI at 3 weeks and 56 (44%) at 9 weeks. In univariate analysis, responders to treatment had higher scores for the IPQR domain treatment control and lower scores for IPQR consequences, depression and pain catastrophizing at both 3 and 9 weeks. Physical and patient related factors, including accuracy of injection and US features, were not associated with outcome, with the exceptions of higher baseline pain and previous experience of injection being associated with non-response at 9 weeks. In multiple regression, treatment control was the only independent predictor of response at 3 weeks. At 9 weeks, treatment control, consequences and depression were independent predictors of treatment outcome.

Conclusion: In this observational study illness perceptions and depression predicted the outcome of IACI at 3 and 9 weeks. By contrast, physical factors including accuracy of injection did not influence outcome. Further work is needed to replicate these findings and elucidate mechanisms for these effects.
Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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I would like to acknowledge the help of numerous people, without whose help the work described in this thesis would never have been completed. Inevitably the list will not be exhaustive.

Before all others, I must acknowledge my profound thanks and gratitude to my wife Nicola and to my boys Sam and Ben, all of who have made numerous sacrifices during this process and on whose support of all kinds I have depended throughout, and also to my parents Robin and Kathy, who have supported me both financially and emotionally.

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Finally I thank the lovely, ever generous patients of the Black Country, without who this work could not have happened and whom I will continue to serve in the future.
Contribution of the student to the work described in this thesis

The student was the principal author of the study and conducted the background literature search, determined study objectives, study design and methodology, selected the instruments to be utilized and designed the study documents including the patient information sheet and consent form and proformas used. Advice was provided in the setup phase by Dr Rainer Klocke and Professor George Kitas. Mrs Elizabeth Hale, Clinical Psychologist provided advice on potential psychological models which could be considered. Mr Peter Nightingale provided statistical advice with respect to power calculations, following direction and data provided by the student.

The student completed all aspects of ethics applications using the online IRAS system, made applications to the ethics committees involved and made any adjustments requested. The student coordinated patient recruitment and appointments and conducted combined screening and baseline investigations including all of the ultrasound scans performed during the study and the assessments for air-arthrosonogram (although not the injections, as described) and conducted a significant proportion of the follow-up appointments. A small proportion of follow-up appointments were conducted by Sue Cadman, biomedical Scientist at Dudley Group NHS Foundation Trust.

The student was entirely responsible for data entry using a Microsoft access database provided by the data management team at the University of Manchester Clinical Epidemiology Unit (which database was designed according to specifications provided by the student) and was solely responsible for subsequent analysis, although advice on analytical strategy was provided by the statistician, supervisors and by Joan Duda, Professor of Sports Psychology at the Institute of Sport and Exercise Sciences of the University of Birmingham in the case of the handling of psychological variables. The student is acknowledged as the first author of each of the results chapters, with revisions being suggested by the supervisors; Professor Terry O’Neil and Dr Rainer Klocke, and by Professor George Kitas in the case of the systematic review. Laboratory samples were processed by the research lab in Dudley by Jackie Smith and Sue Cadman.
Rationale for submission of thesis in alternative format

I have chosen to submit this thesis in the alternative format after careful deliberation and discussion both with my supervisors and with the faculty training manager and with the approval of the approval of the postgraduate director.

The main intention in doing so was to present my results chapters as manuscripts that could be ultimately submitted for publication from the earliest stages of their preparation. As a career clinician returning to my training programme, I was all too aware of the limited time that would be available to me for any comprehensive reformatting would ordinarily be required to submit manuscripts describing my findings to peer reviewed journals and saw alternative format as a method of doing so efficiently. The alternative, I felt, was the risk that I might never succeed in publishing what I believe to be novel and interesting observations that are relevant to clinical practice.

The necessity to constrain the length of each results chapter to one that could be submitted for peer review without significant alteration also compels the author to be succinct from the outset.

Lastly, alternative format submission has allowed me to present the work contained in chapter four, which had already been published, without danger of violating University regulations relating to self-plagiarism.
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Introduction

1.1 General Introduction

Knee osteoarthritis (KOA) is generally considered a largely degenerative arthritis, usually characterised by pain and reduced joint function that results from a combination of genetic and environmental factors including mechanical stress. It is one of the commonest causes of disability in older people in the western world and has both direct effects on the individual in terms of reduced quality of life but also has major health economic implications for society in general. In the absence of reliable methods to prevent the onset of the condition, its prevalence is likely to increase as populations age, which will result in the scale of the problem growing steadily over time. Given the significant health impact of the disease, an important target for research is to determine how the symptoms of patients with osteoarthritis may be best managed and how available treatments may be utilised optimally to achieve this.

1.1.1 Epidemiology, morbidity and clinical impact.

1.1.1.1 Occurrence

Since symptomatic KOA is usually, at some stage of its development, associated with characteristic changes in plain radiographs (which are discussed in section 1.1.5.1), previous estimates of prevalence have been made on the basis of radiographs. In one population survey, using purely radiographic definitions for KOA, the authors reported an estimated prevalence as high as 40% in those over 55 years of age (1). However, it is a well observed and enigmatic feature of OA, that a significant proportion of affected individuals report no symptoms. Thus in the same population, although 40% of patients had radiographic changes, only 12.5% of those over 55 were classified as having symptomatic, radiographic knee osteoarthritis. Further surveys also illustrate that not all knee pain suggestive of OA is accompanied by radiographic change. A comparison of two population surveys suggested that around 25% of those over 55 experience knee pain in a given year (2;3) but only 13 and 19% of the same populations had radiographic KOA as well as symptoms (2;3). One study found that
reporting persistent knee pain in the presence of normal radiographs was associated with higher anxiety (4). What is clear from all studies is that the prevalence of symptomatic, radiographic OA increases with age and is higher in females than in males (5).

1.1.1.2 Morbidity

OA is linked with pain and functional impairment. The World Health Organization estimated that hip and knee OA was the eleventh highest contributor to global disability in a 2010 survey (5). Individual studies demonstrate both the specific contribution of knee OA to this population burden and also the level of difficulty experienced by individuals. Cross sectional studies reflect the disability associated with knee pain (6;7), suggesting that between 14% and 15% of older adults suffer frequent limitation in daily activities and that around 1.6% of the population aged between 65 and 74 are severely disabled by KOA, rising to 3.5% in those over 75(3;8). A Longitudinal study of 111 patients with knee OA demonstrated that in patients referred to secondary care, the condition was associated with the development of on average moderate to severe disability over the eight years of follow-up (9), as assessed by a standard tool, the Health Assessment Questionnaire.

1.1.1.3 Economic cost

The economic costs of knee osteoarthritis, both to the individual and to society, are appreciable. Studies from Canada have placed the annual costs to the individual of disabling lower limb osteoarthritis, in terms of direct costs for healthcare and losses in income, at between 4800 and 9700 USD (10;11). A UK survey estimating the costs of OA in general estimated a figure of £480 for increased annual personal costs alone, excluding loss of earnings (12). Further costs to the health economy are incurred directly by the requirement for joint replacement surgery. In one population survey 3.9% of those over 65 years old had already had knee replacement surgery, while a larger cross sectional population survey found that knee replacement surgery would be appropriate, according to accepted criteria, in 16% of patients identified by
screening as having KOA (13). In a longitudinal UK cohort of patients referred to secondary care with knee OA, 33% had undergone joint replacement surgery after 8 years (9).

The National Joint Registry reported that over 100,000 knee replacements were carried out in the UK during 2014 (14), the most common indication being osteoarthritis. The average cost of knee replacement surgery performed in the US is currently estimated to be 49,500 USD per procedure (higher for revision surgery) and that the total cost of knee replacement operations performed in 2010 was 35 billion USD (15). This figure has already increased by 10 billion USD since 2007, due both to an increase by 15,000 procedures and an increase of procedural costs. In view of the increasing age of the population and the resultant increase in the prevalence of knee OA, this economic burden seems inevitably set to rise.

The commonest symptom cited as the cause of both disability and resulting joint replacement surgeries is pain (16-18). It is possible that effective strategies to manage pain could reduce some of this impact on the wider health economy.

1.1.1.4 Clinical features

Knee osteoarthritis is a condition characterised by a combination of degenerative and remodelling processes of both cartilage and subchondral bone that results in pain, stiffness and loss of function. Symptoms which are commonly reported include pain both at rest and on exercise and grinding mechanical sensations arising from the joint (crepitus). Signs include reduced range of movement, instability and variable swelling. Typically pain increases on use of the joint (in contrast with inflammatory arthritis, in which it may ease with use), although some patients have pain at rest that is sufficiently severe to disturb sleep. Stiffness is reported frequently but is usually of a brief duration (less than 30 minutes) by comparison with active inflammatory arthritis, which is usually greater than one hour. Reported instability, the sensation of the joint ‘giving way’ may result either from genuine mechanical compromise or, more frequently, inhibition by pain of already weakened quadriceps muscle. Swelling of the knee, both due to abnormal accumulation of fluid within the joint (effusion) and chronic alteration of the bony contours may both be reported by patients and
observed on physical examination. Patients with symptomatic KOA may report functional difficulties in a wide range of situations found within daily life including walking, standing from a seated position, climbing stairs, sleeping in comfort and even aspects of personal care such as bathing or toileting. A critical element of patients reporting functional difficulties is pain (19;20).

1.1.2 Classification of knee osteoarthritis

The most widely used classification criteria used for KOA are those of the American College of Rheumatology (21). These were the product of a consensus exercise in which the various symptoms and clinical signs (including radiographic appearances) were integrated, with the intention of being able to clearly distinguish osteoarthritis from other forms of knee arthritis, such as rheumatoid arthritis or gout for the purposes of clinical trials.

In the method recommended by the authors for the identification of KOA cases in clinical trials, the features used are the presence of radiographic osteophytes, synovial fluid features suggestive of OA (or, if this information is unavailable, a surrogate measure of age of 40 years), morning stiffness of less than 30 minutes duration and crepitus. Synovial fluid features of OA in this context are considered to be 1) clear 2) viscous fluid 3) white cell count less than 2000/ mm³. These can be applied in the form of a classification tree, as shown in Fig. 1 overleaf. In the presence of osteophytes the sensitivity was found to be 83% and the specificity 93%. In the absence of osteophytes, the sensitivity was 94% and the specificity 88.
1.1.3 Pathophysiology

The central feature in the process of OA is the degradation of hyaline cartilage within synovial joints. Hyaline cartilage is composed of chondrocytes in an extracellular matrix. Extracellular matrix is a network composed of cross linked collagen fibrils which provide a retaining structure for large chain, negatively charged proteoglycan complexes. Large numbers of molecules of the principal component, aggrecan, are attached to hyaluronan molecules. Collagen provides structural integrity to the network on account of its strength and cross links. Aggrecan, which retains water as a result of its charge properties, resists the transfer of force when the structure is loaded. As a result, hyaline cartilage is able to provide protection to the subchondral bone from mechanical forces relating to joint loading. However, this ability may be
overcome by abnormally great forces acting on cartilage, such as are generated in a mechanically unstable or mal-aligned joint and the structural integrity of the cartilage becomes compromised. Biomechanical factors are a critical factor in lower limb osteoarthritis. This has been demonstrated both in animal models (22;23), in which mechanical destabilisation has been shown to cause rapid gene induction in chondrocytes, and in longitudinal studies of the effect of varus deformity on progression of KOA in humans (24).

The degradation of cartilage in OA is not only a mechanical phenomenon, but is also actively carried out by the proteolytic activity of matrix metalloproteinases, including aggrecanases and collagenases, and results from an imbalance between these enzymes and their endogenous inhibitors (25).

A growing body of research has demonstrated that the imbalance in these processes is strongly influenced by a variety of cytokines produced during inflammation and therefore that inflammation in KOA may have an important role in driving the process of cartilage degradation (25). The source of this inflammation may itself be mechanical processes causing trauma and tissue injury and possibly also resultant cartilage debris. Very rapid onset of synovial inflammation has been demonstrated in experimental models based on surgical joint destabilisation (26;27), with at least some of the process being dependent upon membrane bound FGF2 (23). Interleukin 1-beta (IL1β) has been considered to have a pivotal role in the progression of KOA (28), although this is not universally accepted (29) IL1 β has been shown to have effects on the synthesis of matrix metallo-proteinases (MMPs)and their inhibitors, driving the local environment towards cartilage degradation, and on the local production of interleukin-6 in KOA (30). As well as their effects on MMPs, cytokines also stimulate the production of local mediators including prostaglandins, nitric oxide and reactive oxygen species which both have further detrimental effects on cartilage degradation and contribute to local symptoms, as will be discussed further in the later section relating to pain in KOA.
1.1.4 Synovitis in knee osteoarthritis

It has been increasingly recognised that many patients with KOA report inflammatory ‘flares’ of disease over time as manifested by periods of increased pain and clinically detectable signs of effusion; features which suggest an inflammatory process (31). However, it is now also recognised that the synovium in KOA demonstrates evidence of inflammation even in the absence of a clinical flare. Arthroscopic study of patients with both early and later stage KOA frequently demonstrates evidence of synovitis (32-34). The proportion affected was 50% in one large study of patients with painful KOA (33). Further histological examination of the tissue demonstrates the presence of inflammatory cells that demonstrate the same characteristics of cellular activation and cytokine production as those present in inflammatory arthritis (32;35;36), although they are less pronounced in KOA.

Imaging provides further strong evidence for the overall prevalence of inflammation in KOA. Imaging methods have the advantage of being non invasive, thus avoiding the need for procedures such as arthroscopy and synovial biopsy or bias associated with studies based on tissue obtained from patients undergoing knee replacement surgery, who may represent a particularly symptomatic or severe phenotype. Imaging techniques such as high definition ultrasound (US) and Magnetic Resonance Imaging (MRI) are more sensitive instruments to detect features of inflammation such as effusion and synovial thickening than clinical examination alone (37;38). Appearances of synovial thickening demonstrated using contrast-enhanced MRI have been shown to reflect histological synovitis (39).

A cross-sectional US survey examined 643 patients with painful KOA for features of effusion and synovial hypertrophy (40) using measurement definitions for each that were deemed pathological by consensus (41). 43% of patients had evidence of effusion and 16.7% evidence of synovial hypertrophy. MRI imaging studies demonstrate comparable rates of effusion and synovial hypertrophy and higher rates in those with radiographically advanced disease (42).
1.1.5 Imaging

The following section describes imaging methods in osteoarthritis in more detail.

1.1.5.1 Radiographs

The first form of imaging used to diagnose and classify KOA in routine clinical practice and still the commonest form used is the plain radiograph. This has also long been considered integral to classifying OA from the point of view of clinical trials and epidemiological studies. Established OA produces characteristic changes on plain radiographs including reduction of joint space (a result of the reduced thickness through degradation of articular cartilage) and bone remodelling effects including osteophyte formation (formation of irregular bony spurs and spines adjacent to the articular surface), subchondral sclerosis (thickening of bone in the layer beneath the cartilage) and bone cysts (spaces within subchondral bone). These changes have been characterised within the classification system of Kellgren and Lawrence (KL) (43), which remains the radiographic classification system most commonly used both in clinical practice and research studies, although other systems have been proposed. The KL system recognises 4 grades of OA (with the additional grade 0 representing no radiographic disease as shown in Table 1.
Table 1: The Kellgren-Lawrence OA grading system

<table>
<thead>
<tr>
<th>Grade 0</th>
<th>No discernible abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Doubtful joint space narrowing, possible osteophyte</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Definite osteophyte, possible joint space narrowing</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Moderate, multiple osteophytes. Definite joint space narrowing. Some sclerosis and possible deformity of bone ends</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Large osteophytes. Severe joint space narrowing and sclerosis. Definite deformity of bone ends.</td>
</tr>
</tbody>
</table>

Although widely accepted, there exist appreciable limitations with this classification. The first, and perhaps greatest of these is that multiple descriptions of KL grading have been identified in the literature, without initial acknowledgement of this (44). The table displays the definitions as used by Zhang (45).

A further criticism is that KL grading has been suggested to be too heavily dependent on the osteophyte as both the pathognomonic feature OA and its main determinant of its severity (46;47). This can lead to inconsistent allocation of grade in the case of radiographs with discordant severity of features such as severe joint space narrowing in the relative absence of osteophytes. As a result, alternative grading systems have been proposed that classify the severity of individual radiographic features (48;49). The second limitation of the KL system in the case of the knee joint is that the original description was only applied to the tibiofemoral compartment of the joint and not to the patellofemoral joint. It is now recognized that the patellofemoral joint can give rise independently to symptoms in the absence of significant radiographic change in the tibiofemoral compartment (49;50) and grading scores have been adapted to grade disease of the patellofemoral joint (49;51). A further limitation of the plain radiograph itself in KOA has already been alluded to in section 1.1.5.1: although radiographic grades such as KL are considered to describe radiographic severity, this correlates only...
poorly with severity of symptoms (52). This may, however, relate more to individual variations between patients, since a stronger relationship is shown within patients in studies comparing both knees with discordant radiographic grades than it is between patients (53). Just as radiographic changes can exist in the absence of symptoms, so can symptoms also be present in the absence of radiographic change that can be demonstrated by more sensitive imaging methods such as MRI (54;55).

1.1.5.2 Ultrasound

A major technological limitation of plain radiographs that could provide a plausible explanation for the poor correlation between plain radiographs and symptoms in KOA is that they are unable to image soft tissues. High resolution ultrasound (US) provides a method of imaging soft tissues that allows a much greater sensitivity and specificity for detecting features such as effusion or synovial hypertrophy than clinical examination alone (37), as well as other soft tissue features that may give rise to symptoms such as bursitis and popliteal cysts. Although not capable of imaging beneath the surface of bone, it provides a sensitive method of imaging abnormal features of the surface such as osteophyte in accessible areas.

As well as being able to detect evidence of synovial hypertrophy and effusion, power Doppler US permits the assessment of hyperaemia. Briefly, Doppler US characterises flow in blood vessels by detecting movement towards or away from the probe. In the case of power Doppler US, the single-colour coding of all flowing blood above a set threshold and irrespective of flow direction, provides an index of perfusion within underlying tissues and is particularly sensitive to detecting flow in small vessels. That increased Doppler signal in thickened synovium correlates with histological evidence of inflammation has been established in the case of KOA (56). While abnormal Doppler signals may be demonstrated in knees with symptomatic OA (56;57), larger cross-sectional observational studies do not suggest that this is a common finding (58). The sensitivity of power Doppler may be increased by the use of intravenous contrast agents (59) but such techniques are comparatively expensive and not in routine clinical use.
As an imaging modality, US has the advantages of being widely available, being relatively inexpensive by comparison with techniques such as MRI and providing dynamic images that can be interpreted in real-time. This provides the important advantage that it can also be used to provide accurate guidance and verification for procedures such as intra-articular injection, which will be discussed in more detail in section 1.6.

1.1.5.3 Magnetic Resonance Imaging (MRI)

MRI is a powerful tool for imaging in OA and has the advantage that it can image the whole joint and the areas beneath the bone surface. The basis of MRI imaging relies on the use of a magnetic field and radiofrequency pulses to alter the spin of protons in tissues and the measurement of the signal generated by the protons as they return to their relaxed state. This makes it ideal for imaging soft tissues in which water is abundant, including synovium and cartilage. MRI is effective in detecting meniscal pathology, cartilage defects, ligamentous pathology and synovial thickening (38). MRI has been shown to detect pathology in the majority of patients reporting knee pain, even in the presence of normal x-rays, although these findings are also found less commonly in older adults who do not report knee pain (55).

Contrast enhancement using gadolinium has increased the potential of MRI to provide sensitive methods for detecting and quantifying synovitis in osteoarthritis beyond what may be achieved by unenhanced techniques (60;61). Studies employing MRI have provided strong evidence that synovial hypertrophy and effusion are both extremely common in symptomatic KOA, as discussed in section 1.1.4.

1.2 Pain in knee osteoarthritis

The following section outlines the mechanisms of pain and pathways of nociception in knee osteoarthritis and discusses other contributory factors including the role of synovitis, bone marrow lesions and psychological factors.
1.2.1 Mechanisms of pain in knee OA are linked only indirectly to pathophysiology

At the centre of the consideration of pain in knee osteoarthritis is a confusing lack of correlation between symptoms and key features of pathology. This has resulted in a degree of separation between research into structural progression and research into symptom relief. While the degeneration of hyaline cartilage and its sequelae may be a critical step in the pathophysiology and progression of OA, it had previously thought that cartilage was aneural. More recent research suggests that this may not be entirely true in established OA, as disrupted cartilage may be subject to neovascularisation and even innervation (62).

1.2.2 Pathways of nociception in knee OA

The structural details of the pain sensitive (nociceptive) elements of the nervous system, the neurotransmitters operating within these neurones and factors which influence their functions and the structural lesions that may give rise to pain in knee osteoarthritis are summarized in reviews of the subject (63-65). The principal neurones involved in nociception are the small fibres with free nerve endings and very small unmyelinated fibres (known as Aδ and C fibres respectively) (see Fig 2). These are characterised by having a high threshold for activation, which means that they require a high level of stimulation to activate them, and by the use of the neurotransmitters substance P and calcitonin gene related peptide (CGRP). Anatomical as well as immunohistochemical studies based on these neurotransmitters have suggested that nociceptors are present in the periosteum, ligaments, subchondral bone and the external layers of the meniscus (66;67). They have also been demonstrated in the synovium, although inconsistently and it has now been suggested that they may also enter cartilage as pathology disrupts the usual bone-cartilage interface (62).

These fibres join the central nervous system in the dorsal horn of the spinal cord, at which point their output signals can be subject to influences including inhibition by inputs from inter-neurones. From the dorsal horn, nociceptive signals are transmitted via the spinothalamic tract to areas of the central nervous system connected with pain.
processing. These centres comprise two systems; the lateral and the medial system. Both involve nuclei within the thalamus. The lateral system terminates within the somatosensory cortex and is concerned with features of pain such as site, severity and quality. The medial system, by contrast, terminates in midline nuclei of the thalamus as well as the amygdyla and is concerned with aspects of pain such as emotional and affective content, as well as learning (64). A study that used Fludeoxyglucose Positron Emission Tomography Scanning (FDG-PET), a type of brain imaging that is able to examine the brain’s local metabolic activity in experimental situations, showed that these areas of the brain associated with affect and learning were activated in the presence of arthritic knee pain but not in experimentally induced knee pain (68). This demonstrates that pain processing is complex and operates beyond the level of physical sensation, an idea that will be discussed in a further section 1.2.5.

Emotional processes related to pain

Discrimination of pain

Medial System; midline thalamus, amygdyla

Lateral System; somatosensory cortex

Lateral spinothalamic tract

Dorsal horn of spinal cord

Aδ fibres, C fibres (periosteum, ligaments, bone, synovium)

Interneurones potentially provide inhibitory input

Inflammatory Mediators sensitize peripheral neurones

Structural pathology, mechanical stimulation

Figure 2; simplified scheme of nociceptive pathways operating in knee osteoarthritis
Several characteristics of the nervous system affect the way in which pain is reported and help to explain the way in which pain sensation can become altered in a chronic context such as knee arthritis. All relate to the fact that the nervous system is dynamic, adapting the way that it operates in response to its environment and inputs.

Nociceptive neurones can adapt in a number of ways. One way in which this can occur is through ‘wind-up’, in which repeated stimulation by a noxious stimulus leads to an increased output. In the local environment the size of the receptive fields of nociceptors (the area of tissue from which a nerve reports stimuli) can increase, giving rise to pain from areas adjacent to the original source of the stimuli. Factors indicative of local damage can lead to the recruitment of previously ‘silent’, high threshold nociceptors, increasing the number of neurones available to report pain and further increasing signals to the dorsal horn. Importantly, it is also known that the threshold of nociceptors themselves are highly variable and can be influenced by a variety of factors that can be present or released into tissue including prostaglandins, Vasoactive Intestinal Peptide, CGRP, cytokines including IL6 (69-71) and tumour necrosis factor α (TNFα) (69;70;72-74). The result of this sensitization is that stimuli including mechanical stimulation which were previously innocuous now become noxious (75;76), giving rise to abnormal conditions of pain sensation such as hyperalgesia (increased sensitivity to pain) and allodynia (pain in response to stimuli not normally associated with pain). One of the unifying features of these sensitizing factors is that they are released in abundance in inflammation.

1.2.3 The role of Inflammation in OA pain

As discussed in section 1.1.4, subclinical synovial inflammation in KOA is common. Inflammation results in the release of many products that are capable of increasing the sensitivity to pain by direct and indirect effects, both locally and centrally (65). While the effects of individual mediators have been demonstrated both in vitro and in
models, further evidence of the link between local inflammation and pain in OA is provided by studies using MRI.

MRI imaging studies demonstrate that although small effusion may be detectable even in patients with neither pain nor radiographic OA, moderate and large effusions are more common in patients with painful, radiographic OA (42). Synovial hypertrophy was found in all 107 patients with painful, radiographically advanced OA (KL>3) who were examined in one study (42), in 73% of the 267 patients with painful OA with less advanced radiographic disease and even in 52% of those with radiographic OA but no pain.

Furthermore, although synovitis and effusion can exist in the absence of pain, MRI studies using both cross sectional and prospective cohort methodologies (42;77) found associations between these features and pain severity. Longitudinal studies correlating changes in appearances of synovial inflammation over time with changes in levels of reported pain provide important evidence to support a causal relationship between anatomical features and pain. These studies are summarised two systematic reviews (78;79). A recent study using ultrasound did not find that features of inflammation including effusion and synovial hypertrophy were predictive of pain severity (80). There were, however, a number of limitations to the study which may have contributed to negative findings including an ultrasound protocol examining only limited areas of the knee joint, a definition of synovial hypertrophy that might be considered within normal physiological limits, a smaller proportion of patients showing features of effusion or synovial hypertrophy than other studies and possible selection bias.

1.2.4 Bone marrow lesions

The contribution of MRI imaging in determining the causes of pain in knee OA has not been limited to the evaluation of features of inflammation. A further major contribution of MRI has been to describe the characteristics of a feature called ‘bone marrow lesions’. Zanetti defined bone marrow lesions as “ill-defined hyper-intensities
seen on short T1 inversion-recovery images and on fat-suppressed proton density and T2 weighted fast spin echo Magnetic Resonance Imaging” (81). These lesions had previously been described as ‘bone marrow oedema’ but studies of their histology suggest that they contain areas of oedema only infrequently and are more likely to represent areas of bone remodelling (81;82). This theory is supported by the fact that medial bone marrow lesions are more prevalent in knees subject to dynamic varus deformity (ie where the medial area of the knee is subject to increased mechanical stress) (83). Under physiological conditions, bone remodelling according to increased stress is anticipated although, in contrast to in OA, this process is not usually painful. Bone marrow lesions are rare in knees without OA but common in those with KOA (55). Their frequency increases with increasing radiographic severity of osteoarthritis and, for a given grade of OA, they are more common in a painful as opposed to a non-painful knee (84).

In longitudinal studies of KOA (84;85) change in size of bone marrow lesions has been shown to be associated with changes in reported pain. Larger bone marrow lesions are found much more commonly in those with significant cartilage defects and significant knee pain (86). Systematic reviews found evidence for the positive association between bone marrow lesions and pain in knee OA (78;79).

1.2.5 Psychological factors and pain reporting in osteoarthritis

While identifying physical mechanisms by which pain originates is critical to understanding how a condition may be painful, an examination of the experience and reporting of pain in any condition is incomplete without consideration of psychological factors. As previously described, pain sensation is accompanied by activity within areas of the brain concerned with affect and emotional responses. It is well recognized, according to the biopsychosocial model of pain (87), that psychological factors play a considerable role in determining an individual’s experience of pain and that there is a dynamic relationship between pain and affective states.
A number of psychological dimensions have been shown to affect reporting of pain in people with arthritis in both cross sectional and longitudinal settings (88;89). Factors which have been shown to have associations with pain reporting in osteoarthritis include measures of psychological distress including depression and anxiety, cognitive variables that determine the way in which an individual relates to pain and coping strategies (90). The literature considering the role of some commonly studied psychological dimensions is considered in the following sections.

### 1.2.5.1 Depression and anxiety

Several studies have suggested associations between measures of psychological distress and OA pain. Wolfe et al demonstrated an association between depression and higher pain scores in a cross sectional survey of 655 patients with lower limb osteoarthritis (91). Similar associations have been shown in other cross sectional studies of patients with KOA (92;93). These cross sectional data do not provide proof that depression causes increased perceived pain, however, since chronic pain may itself result in psychological distress. An alternative interpretation could be that patients who experience higher levels of pain experience more depression. A prospective study of 88 patients with OA provided better evidence for causation by demonstrating a significant association between elevated anxiety scores at baseline and increased pain in the following week, with anxiety explaining 13.8% of the variance in pain (94). The effects of depression seen in this study were significant but smaller than those of anxiety. A prospective cohort study of the health effects of intensive intervention to treat depression compared with normal care examined the effect of treatment on reported pain due to osteoarthritis in almost 1000 patients over 12 months and demonstrated a statistically significant reduction in pain in the intervention group (95). While the difference between groups was modest in clinical terms, the effect may have been underestimated since all patients, including those in the ‘standard care’ group, were being actively treated for depression.
1.2.5.2 Self efficacy

Self efficacy, as defined by Bandura (96), refers to an individual’s belief that they can successfully affect the outcome of a given situation. Studies have examined patients’ pain-specific self-efficacy in both cross sectional and longitudinal settings. These demonstrate that great variations in levels of self efficacy exist between patients and that higher levels of self-efficacy are associated with lower levels of reported pain as well as lower levels of psychological distress (97-99). In the case of knee OA, a cross sectional study of 174 obese patients suggested that self efficacy for pain accounted for 14% of variance in reported pain (100) and a second study of 50 patients with knee OA undertaking physiotherapy found strong correlation between self-efficacy for pain and reported pain intensity (r=0.5) (20).

1.2.5.3 Pain coping strategies

Pain coping strategies were defined by Lazarus and Folkman as cognitions or behaviours used by an individual to reduce stress (101). They may also be considered as strategies used by an individual that facilitate adaptation in the face of a stressor such as pain (in which adaptation refers to outcomes such as well-being, depression or physical function). Classification of coping strategies remains problematic. They are often summarily classified as adaptive or maladaptive. Lazarus and Folkman defined coping strategies broadly as either cognitive focussed or emotion focussed (101). Cognitive focussed coping is characterised by gaining information about a problem and trying to devise active strategies to negate or reduce the effects of the problem. Emotion focussed coping is characterised in trying to reduce the emotional effects of a stressor.

Various tools have been used to measure coping, including the ways of coping scale (101), the Vanderbilt Pain Management Inventory (102) and the coping strategies questionnaire (CSQ) (103). The coping strategies questionnaire is arguably the most comprehensive and widely used measure of pain coping strategies and made the distinction between cognitive coping strategies and behavioural coping strategies, as well as an appraisal of self-efficacy. The cognitive strategies identified by the questionnaire include diverting attention, reinterpreting pain sensations, coping self-
statements, ignoring pain, hoping or praying and catastrophizing. It can be seen that some of these could be defined as problem focussed and some emotion focussed. The behavioural strategies identified in the questionnaire were increasing activity level and increasing pain behaviours.

In general, use of problem focussed cognitive strategies is considered adaptive and is associated with lower levels of reported pain than where other strategies are used. This was demonstrated in rheumatoid arthritis both for pain on the same reported day (104) and on pain reported on the day following baseline measurement (105). In 51 patients with KOA, high scores for the CSQ factor “pain control and rational thinking” were found to be associated with significantly lower levels of reported pain in cross sectional analysis (106). However, the assumption that problem focussed coping is always adaptive is over simplistic. In keeping with the transactional model of stress and coping of Lazarus and Folkman, the success of such strategies in terms of adaptation depends on the individual’s perception of being able to execute them in the face of the stressor in hand and appraisal of their success. Fang showed that active, problem focussed coping resulted in higher stress than emotion focussed coping in a cohort of women with elevated risk of ovarian cancer since active coping strategies could not reduce the risk of this cancer (107). By contrast, in a study of heart disease, active coping would be likely to be successful. The success of different strategies in given situations complicates the comparison of studies of pain coping across different situations and makes generalised conclusions challenging.

1.2.5.4 Pain related fear

Pain related fear anxiety or avoidance refers to a situation of heightened attention to pain sensation and anticipation of pain, particularly when undertaking physical tasks. It has been studied longitudinally in the general population, where higher scores predicted increased severity and chronicity in those patients who developed back pain (108) and also predicted increased pain-related disability in patients in primary care.
who already had low back pain (109). By contrast, a study of patients with knee OA demonstrated that although pain related fear was related to psychological disability and reduced walking speed, it was not an independent predictor of pain (110).

### 1.2.5.5 Pain catastrophizing

Pain catastrophizing refers to “a highly negative mental set in response to anticipated or actual pain” (111). It comprises domains of rumination (constant contemplation and consideration of pain), magnification (increased perception of severity of pain) and helplessness (perceived inability to take any action to reduce pain severity). It was initially considered as a coping strategy but subsequent authors have suggested that it may more accurately be described as a set of pain related beliefs (112).

In cross sectional studies, higher pain catastrophizing has been shown to be associated with increased pain severity in KOA (113) as well as in other medical conditions. It has also been shown to reduce the threshold to pain in response to laboratory pain stimuli in patients with knee OA (114). In patients with rheumatoid arthritis, baseline levels of pain catastrophizing at baseline were predictive of reported pain intensity at 12 months (115).

Pain catastrophizing shares similarities with other measured psychological concepts including depression. Controversy exists in the literature with regard to the extent of the overlap between pain catastrophizing and depression, since both relate to negative cognitive appraisals and have been shown to be strongly correlated (116). Some authors have questioned whether the two are in fact sufficiently independent to avoid the accusation of concept redundancy (117). However, a prospective cohort study of 632 patients with sub-acute pain by Linton (118) demonstrated that pain catastrophizing and depression, while showing correlation, operate independently. This was demonstrated since firstly patients were found to show high scores for depression but not catastrophizing and vice versa. Secondly, patients showing evidence of both depression and catastrophizing demonstrated worse pain outcomes than those with only one of the two problems. Keefe et al (119) demonstrated the
independence of the constructs, while acknowledging correlation between them, in a prospective longitudinal study of 168 patients with KOA that assessed pain catastrophizing and depression at baseline and after two years. The results demonstrated that reported levels of pain at two years were higher in females and that this effect was mediated by catastrophizing (i.e. female gender predicted higher catastrophizing, catastrophizing and female gender predicted greater pain and there was no significant relationship between gender and pain once catastrophizing was adjusted for). Although depression was also correlated with catastrophizing in this study, catastrophizing still mediated the relationship between gender and pain at two years after adjustment for depression. This provides evidence suggesting that pain catastrophizing is independent of depression.

The example of pain catastrophizing raises a more fundamental question about the role of psychological constructs in relation to pain. Psychological research is characterised by competing models seeking to explain similar observations. Combining constructs from across different models can lead to conceptual overlap which can be problematic for prediction models, leading some authors to suggest a reductionist approach to explaining variance in pain based on factor analysis (120). Since it is statistically derived rather than underpinned by a unifying psychological framework, this approach does not lend itself to interventions to alter clinical outcomes. However, this work serves as a reminder to be cautious about assuming disparate psychological variables across differing frameworks to be completely independent where the goal is to predict and modify outcomes to treatment.

In conclusion, there is considerable evidence to suggest strong relationships between psychological factors and levels of reported pain in rheumatic diseases and in knee osteoarthritis specifically. These effects have been demonstrated both in cross-sectional studies and also in longitudinal studies, which provide some stronger evidence for causation.
1.3 Treatment of pain in osteoarthritis

Pain is arguably the most debilitating symptom of osteoarthritis and a priority for patients with the condition (12). Since no approved disease modifying treatments for OA are currently available (121), treatment of pain is the most commonly employed strategy. Modalities employed include lifestyle measures, physical therapy techniques, analgesic medication, intra-articular injections including corticosteroids and surgical management and are outlined in this section. Several professional organizations have produced evidence based recommendations for the management of pain in knee osteoarthritis, including the European League Against Rheumatism (122;123), the American College of Rheumatology (124) and the Royal College of Physicians (125). The following section reflects these guidelines.

1.3.1 Lifestyle modification

Current UK guidelines for managing osteoarthritis advocate lifestyle modification including regular aerobic exercise ‘irrespective of their age, co-morbidity, pain severity and disability’ (126) and weight reduction. These measures have been shown to reduce pain and improve function in knee osteoarthritis (127). However, motivation to exercise in the face of these limitations can be difficult to achieve and a recent UK survey has revealed that 44% of those with OA do no exercise at all, despite self reports of improvements in pain those who do (12).

1.3.2 Joint Specific Exercises

In addition to general exercise, a systematic review and meta-analysis conclude that exercise programmes can reduce pain and improve function in patients with knee OA (127;128). The exercise programmes showing most benefit to patients are those that include elements of muscle strengthening, flexibility and aerobic fitness and may be either land or water based (128). Patients can be taught these exercises by a physiotherapist, although commonly available information booklets also contain instructions. To preserve benefits exercises need to be continued but long term concordance is known to be poor (129).
1.3.3 Oral and topical analgesics

Pharmacological treatment of pain in osteoarthritis is based on generic treatment strategies, now reinforced by evidence from clinical trials, rather than specific consideration of the pathophysiology of pain in OA.

Paracetamol the first recommended oral analgesic for use in knee OA according to all of the guidelines cited above (122;126). Its preference over other medication is the result of evidence of efficacy with regard to treating pain, balanced against a favourable profile of side-effects and risks. Although often dismissed by patients, perhaps since it is readily available without prescription, a EULAR standing committee found evidence that “it could be used effectively in doses of up to 2600mg/day for two years without significant adverse outcomes; ...the efficacy of paracetamol was similar to that of naproxen 750mg/day” (113). However, emerging evidence suggests that it may not be as safe as previously supposed, from the point of view of both gastrointestinal and cardiovascular side effects (130), which led to draft guidance on the management of OA by NICE to limit its use (131), later retracted in the face of stakeholder feedback.

Non Steroidal Anti-Inflammatory Drugs (NSAIDS) reduce local inflammation by inhibition of cyclo-oxygenase (132). They have long been used to treat pain in osteoarthritis. Consciousness of their gastrointestinal, renal and most recently cardiovascular toxicity has led to a reduction in their use as oral agents in the management of knee pain (133-135). However, their efficacy as topical agents has been demonstrated in clinical trials (136;137) and their use is supported by existing guidelines (138;139). NSAIDs, including oral preparations, are still recommended within guidelines for patients who fail to respond to paracetamol analgesia (122;126).

A further topical agent advocated is capsaicin cream. Derived from chilli peppers, capsaicin has been shown to desensitize nociceptive C-fibres, thus providing analgesia if used regularly (140;141). It has been shown to be both safe and effective in clinical trials and was recommended for the treatment of pain in knee osteoarthritis by the 2003 EULAR guidelines (138).
Opioid analgesics, including codeine, tramadol and buprenorphine are widely used for the treatment of pain associated with knee osteoarthritis, frequently in combination with paracetamol. A review of evidenced-based treatment recommended their use in patients in who NSAIDs were ineffective or contra-indicated (119). In clinical practice it is common for patients to use opioid drugs in combination with both paracetamol and NSAIDs.

For some time, antidepressant drugs that alter neuronal function by altering the uptake of neurotransmitters have been used to treat chronic pain. It is not clear in clinical practice whether the efficacy of these drugs is due to their effects on peripheral neurones or via their role in treating depression. An example of such a drug which has been trialled in KOA is the serotonin-noradrenaline reuptake inhibitor duloxetine. Placebo controlled trials of duloxetine in KOA showed that patients treated with duloxetine were more likely to report both significant improvements in pain than placebo (142). However, duloxetine also produced side effects that necessitated significant numbers of patients to discontinue the drug. A recent update of the ACR knee OA guidelines was not able to recommend duloxetine on the basis of current evidence (124).

1.3.4 Surgical management of knee osteoarthritis

Surgical management of knee osteoarthritis is reserved for those patients in whom conservative management has failed (126). The most commonly employed surgical techniques remain arthroscopic surgery including debridement of cartilage and microfracture, high tibial osteotomy, and partial or total joint replacement. New techniques including cartilage transplant and joint distraction (143) (physically reducing the mechanical interaction between the elements of the joint using external fixation devices) are used in some centres and show promising results but are not yet in widespread use.

Joint replacement surgery includes the excision of the diseased portion of the joint and replacing it with prosthetic elements composed of metal or composite materials. It
remains the most effective method of treating severe symptoms of knee OA. The indications for this procedure are severe pain that cannot be managed by conservative methods and severe joint instability.

While these techniques are effective, they carry some disadvantages. Firstly, they are expensive. Joint replacement in particular carries with it the risks of surgical procedure including anaesthetic risk (which may preclude surgery in some patients), risk of infection and failure of prosthesis, with the requirement for revision. It is recognised that joint replacements are subject to wear and an increasing failure rate over time that is increased by the patient’s activities (for instance, continuing a manual occupation is usually not possible) and body mass. Failed prostheses require revision, which is a technically more difficult and more expensive procedure than primary replacement.

In order to reduce the rate of failure of prosthesis, joint replacement is seldom recommended for patients below the age of 60 years or for those continuing manual employment and efforts are often made to defer replacement using other treatment modalities including increased analgesia and periodic intra-articular injection of corticosteroids, which are the subject of the following section.

1.4 Intra-articular corticosteroid injections in knee osteoarthritis

1.4.1 Overview

Intra-articular steroid injections (IACI) have been used for decades in both primary and secondary care for the treatment of symptoms in knee osteoarthritis. The technique consists of the injection of a long acting corticosteroid, usually in conjunction with local anaesthetic, to the intra-articular space under aseptic precautions. Injections are performed without the requirement for hospital admission and have few reported complications. The most severe of these is intra-articular infection, which has been quoted to occur in around one in 15,000 procedures (144) (although these figures also take into account patients with inflammatory arthritis, who have a higher natural
incidence of native joint septic arthritis and some surveys have suggested much lower estimates (145)).

1.4.2 Efficacy of intra-articular corticosteroid injections in knee osteoarthritis

The efficacy of IACI in improving knee osteoarthritis pain has been the subject of several systematic reviews, including one by the Cochrane Collaboration (146-148). All these reviews summarised a similar pool of evidence and concluded that IACI are more effective than placebo in reducing pain for up to three weeks after treatment. Meta-analysis of longer term studies is hampered by differences in study methodology including outcome measures and time points for observed outcome. More recent placebo controlled trials have demonstrated efficacy at 4 weeks (149). In addition, some pooled data from existing trials examined within the meta-analyses suggest that IACI may be effective in reducing pain for up to 24 weeks after treatment (146). The Cochrane review calculated an effect size for IACI at one week of -0.83 (large effect). It also provided a figure of between three and four as number-needed-to-treat for clinically significant improvement in pain at one week.

1.4.3 Variability in responses to intra-articular knee osteoarthritis

Both randomised controlled trials and meta-analyses provide evidence for the efficacy of treatments based on mean differences between experimental groups. What mean differences fail to represent is that very great differences in responses may exist between individual patients. It has long been recognized that such variation exists in the context of the response to IACI in knee OA (150-152). These differences are reflected in large standard deviations associated with mean improvements in pain following IACI reported in clinical trials (153). The reasons behind these large differences in response between patients have long interested clinicians and researchers. If factors determining which patients would respond best to IACI were understood then the treatment might be targeted more effectively at these patients.
1.4.4 Previous studies of predictors of response to steroid injection in knee osteoarthritis

A number of studies have been undertaken looking at factors associated with response to IACI. Although some of the investigations were designed to specifically address the question, most were post hoc analyses of randomised controlled trials examining the effectiveness of IACI against placebo. Factors examined as potential predictors included patient related factors including age and body mass index (58;153-156), radiographic severity, presence of effusion (153;154;157;158), ultrasound evidence of effusion or synovial hypertrophy(58;159). The findings from the individual studies do not point to any consistent predictor of response and indeed in relation to inflammatory characteristics such as effusion and synovial hypertrophy the data are somewhat inconsistent, with some studies suggesting that more severe disease (in this case presence of effusion) predicted better treatment response (153;154) while others indicate that less severe disease (absence of synovial hypertrophy) predicted better response to treatment (159). At the time of drafting this background introduction chapter there were no systematic reviews which attempted to summarise or pool these data; and because of this undertaking a SR was identified as one of the aims of the thesis. The results are presented in chapter three. Subsequent to this review being published a further review has been published (160).

1.4.5 Other Predictors

As well as the relative paucity of data concerning individual putative predictor variables there are no data looking at the role of structural factors other than US and radiographic change, a single study that has examined a possible role for psychological factors in predicting response (157) and there a very limited data concerning a key treatment related factor; accuracy of injection (161). Exploration of these latter two factors is a key focus of the thesis and the rationale underpinning why these factors may be important is explored in detail in the next section.
1.5 Psychological factors and response to therapy in osteoarthritis.

As explored in section 1.2.5, psychological factors are known to be important in explaining variance in pain in OA.

The following section provides an overview of literature of the separate but related subject of the relationship between psychological factors and outcome of therapeutic studies in OA. One of the key hypotheses which will be tested in the thesis is that psychological factors explain variation in pain response following IACI. A number of psychological factors will be considered as putative predictor variables including distress and poor mental health, depression, pain catastrophizing, self efficacy and illness perceptions; these will be considered in turn.

1.5.1 Psychological distress/ poor mental health

A commonly used, if ill defined, measure of psychological ill health applied in the literature relating to orthopaedic surgery in both prospective and retrospective studies has been the mental component score or mental health component of the Short Form 36 (SF36) health assessment questionnaire or similar instruments. Primarily a composite measure of depression and anxiety, but also correlated with both pain catastrophizing and maladaptive coping strategies (162), its frequent use and relatively consistent relationship with outcomes of orthopaedic surgery at various time points provides compelling evidence of the influence of mental health on surgical outcomes.

At least twelve studies have examined the effect of baseline SF36 scores on outcomes following knee or hip surgery (162-173), three studies have examined the effect of the Short form 12 (SF12) (174-176), three have examined combined Hospital Anxiety and Depression Scale (HADS) score (172;177;178) and at least one using the EuroQuol 5D (EQ5D)(179)

Predominantly studies have observed an association between lower (i.e. worse) SF36 mental component scores preoperatively and poorer outcomes in terms of physical function (164;167) or composite measures of pain and function (162;163;165;170). Some studies have observed no difference in functional outcomes (166;169;171) and
one study actually demonstrated greater improvements in pain and function following total hip replacement (THR) and total knee replacement (TKR) in distressed patients, although the scores for pain and function after two years were still worse than in non-distressed patients (168).

Poorer SF12 mental component scores were found to predict higher pain and poorer function at 8 and 24 months post TKR (174). Poorer mental health as measured by EQ5D was found to predict lower pain reduction a year after THR (179).

Two studies using total HADS score as a measure of distress did not show a relationship between distress and changes in function post TKR in 40 patients (177) or satisfaction post TKR in 44 patients (172) but a study of 449 THR and TKR did show a key role for distress in predicting overall self-rated health following surgery in which the effects of self rated physical and social well being on self rated health were mediated by mental health (178)

Overall, studies examining the relationship between mental health and TKR showed an adverse effect of baseline distress on outcome more frequently than did studies of THR. In particular, there was stronger evidence that distress predicts poorer functional outcomes post TKR than post THR.

Several investigations have examined the relationship between baseline mental health and satisfaction following joint replacement. Poor SF12 mental component score was found to predict lower score for satisfaction post TKR (175;176). Two large studies showed the same relationship between poor EQ5D (179) and SF36 (173) scores and lower satisfaction at one year post THR and TKR/THR, although the effect sizes were small. This may suggest that a much smaller study using SF36 failed to demonstrate the same relationship with satisfaction because of lack of adequate power (172). The majority of studies, therefore, demonstrated that poor pre-operative mental health predicted lower postoperative satisfaction. It is worth noting that these investigations included final scores for pain and function in analyses as predictors of satisfaction. This means that mental health has additional effects on satisfaction independent of those mediated by changes in pain and function.
While the literature provides evidence of a relationship between greater levels of distress and poorer outcomes to treatment, the composite nature of the measures such as the SF-36 mental component score is a problem for a researcher intending to conduct an intervention; they are not underpinned by a psychological framework that would inform an intervention. The same limitation does not exist for depression.

1.5.2 Depression

Specific study of the effect of depression on the outcomes of joint replacement surgery has been undertaken less commonly than for more generic mental health instrument scores, which are essentially composite measures encompassing elements of depression and anxiety. However, these studies have in general found depression to predict poorer outcomes following joint replacement, although not always independently of other psychological predictors.

Retrospective studies of registry data suggested that a diagnosis of depression was associated with greater pain 2 years after THR (180) and 1 year post TKR (181). A relationship between higher depression score preoperatively and greater pain at 1 year post TKR and TKR/THR was found in studies using the Beck Depression Inventory (182) and HADS (183) and between depression and both pain and function at 6 months in a study using the Depression Anxiety and Stress Scale 21 (184).

A high quality prospective study of 1991 patients undergoing TKR demonstrated that depression, as measured using EQ5D, predicted poorer outcomes in terms of patients reaching acceptable symptom state and improvements in pain (185).

One study of 79 THR did not find any effect of preoperative HADS score on change in WOMAC score (186). However, the HADS depression subscale explained 3.4% of variance in Oxford Knee Score at 6 weeks and 6% of variance at one year in 100 patients post TKR, after adjustment for baseline variables (187). Two studies examining the effects of depression, as measured using the Patient health questionnaire (PHQ9), on outcomes of TKR failed to demonstrate an effect independent of pain catastrophizing (188;189). This suggests that depression may not operate
independently from pain catastrophizing in this context. However, a smaller study by Edwards which examined global pain at time-points up to a year after TKR showed the converse; that depression predicted pain independent of catastrophizing (190). The reason for the difference in results may lie in Edwards’ use of the Center for Epidemiological Studies Depression Scale (CES-D) and Coping Strategies Questionnaire (CSQ) to measure depression and catastrophizing respectively, as opposed to Sullivan and Riddle’s use of PHQ9 and the Pain Catastrophizing Scale.

Two studies (in addition to Jones (157)) have examined the effect of depression and poor mental health on the outcome of non-surgical treatments for OA. A study of 250 patients with knee or hip osteoarthritis found that depression (as determined by HADS) was a predictor of non-response to a 4 week rehabilitation programme, where response was defined as 18% improvement in pain (191). Poor mental health (also defined using total HADS) predicted non-response to exercise therapy and manipulation at six weeks in 131 patients with hip osteoarthritis, although not at 18 weeks (192).

1.5.3 Pain Catastrophizing

The concept of pain catastrophizing has been described in section 1.2.5.5. There exists strong evidence in the literature that supports a relationship between pain catastrophizing and the outcome of technically successful joint replacement surgeries, in which high scores for pain catastrophizing are associated with poorer outcomes. A recent systematic review concluded that there was strong evidence that pain catastrophizing predicted greater pain following knee replacement surgery (193).

As discussed above, two studies of knee replacement failed to find depression to predict outcome independent of pain catastrophizing, but both studies demonstrated that higher pain catastrophizing at baseline predicted greater pain at 6 weeks (189), 6 months (188) and 1 year (194), independent of the effect of depression. By contrast, Edwards did not find catastrophizing to predict pain post TKR independent of depression (190). Other studies of more limited quality have also shown relationships
between higher pain catastrophizing and both early post-operative pain (195) and postoperative pain at one year (196). In relation to outcomes following TKR, a further study showed a similar relationship between the related concept of helplessness and poorer WOMAC score (197). Overall, the literature provides strong evidence that higher pain catastrophizing preoperatively predicts poorer improvements in pain following TKR.

1.5.4 Expectations of outcome

Expectations relate to the either general or more specific beliefs held by an individual about the outcome of a particular event or treatment. Measurement of expectations has been achieved in various, generally non-validated, ways in studies of orthopaedic surgery ranging from single items asking generally about expectation, a selection of Likert scales relating to specific expectations to completion of standard symptom instruments to indicate the anticipated level of pain and function after a procedure. This degree of heterogeneity across studies makes direct comparison and thus conclusions difficult.

Higher expectations of pain relief were found to predict greater improvements in pain and function 6 months after arthroplasty in one study (198) and to be modestly predictive of pain and strongly predictive of function in a larger international prospective cohort of patients undergoing TKR (16). A study examining the relative contribution of patient expectations and pain catastrophizing to outcomes following TKR suggested that outcome expectations of reduction in pain or improvement in function were not predictive of pain severity. Expectations of better social and domestic function were, however, not just predictive of pain outcome but also partially mediated the effect of pain catastrophizing on pain final severity (194).

Higher expectations were not found to be predictive of satisfaction in a further study of TKR in which follow-up pain and function scores were included in the analysis as possible sources of variance in satisfaction (199). However, although the study did not
seek to determine predictors of pain and function postoperatively, it should be noted that baseline expectations of pain and functional improvement were highly correlated with pain and function at each point of follow-up. A large prospective study of THR (170) found no relationship between expectations and pain and functional outcomes, although the method used to assess expectations in this study was poorly described and appeared to be a single VAS score for global expectation. Overall evidence that expectations act as predictors of outcome following THR or TKR appears, therefore, mixed.

Several studies have addressed the effect of expectations on the outcome of acupuncture treatments. Acupuncture is a controversial treatment and its use in knee OA is not endorsed by British guidelines (200), however it is still used widely both in the UK and internationally. A meta-analysis of the placebo effect in randomised controlled trials demonstrated a moderate placebo effect size for acupuncture of 0.71 (201). In a study of 455 patients with knee OA, patients were randomised to receive acupuncture or sham acupuncture and then further randomised to receive treatment from practitioners who communicated high expectations of treatment or those who communicated neutral expectations (202). While there was no difference shown between acupuncture treatments, both were superior to no treatment. Therapists communicating higher expectations led to greater reductions in pain and greater satisfaction with treatment at three months after treatment than those communicating neutral expectations, with effect sizes of 0.22 and 0.25 respectively. A second study examining treatment expectations in relation to outcomes included 352 patients randomised to advice and exercise, with or without acupuncture (203). Patients with high expectations of the treatment they received (whether they had acupuncture or not) were almost twice as likely to be classified as ‘responders’ according to OMERACT-OARSI response criteria as those with low expectations at six months (OR 1.7, 95% CI 1.06,2.79) or 12 months (OR 1.9, 95% CI 1.13,3.13). However, there were no significant differences in pain score between the groups with high and low expectations over time, suggesting that the differences in OARSI response rates may have related more to changes in self reported function or global score. A larger study, however, which pooled results from over 800 patients receiving acupuncture,
including over 200 with knee OA, did show that patients with higher expectations of treatment effectiveness were over twice as likely to experience a 50% reduction in pain at the end of a course of treatment compared to those with lower expectations (204).

1.5.5 Self efficacy

Self efficacy has been defined in section 1.2.5.2. Higher self efficacy has been shown to predict functional outcomes following joint replacement surgery (183;205;206). In one study the self efficacy rating at 6 weeks postoperatively provided a much better predictor of six month outcomes than the preoperative value (205). By contrast, studies that have examined self efficacy in conjunction with other psychological predictors including pain catastrophizing, coping and mental health (184;188) have failed to demonstrate independent predictive effects on outcomes.

1.5.6 Illness perceptions

Illness perceptions, or health beliefs, are internal representations or models that an individual forms with respect to a specific illness. These representations determine how the individual relates to their illness, what actions they feel are appropriate with regard to it and what strategies or coping mechanisms they employ to manage it. A model that is widely used to describe the operation of illness perceptions is Leventhal’s Common Sense Model (figure 3) (207). In this model illness perceptions are formed in response to simultaneous cognitive and emotional processes. The inputs into these processes may include experiences that the individual has had, sources of information from friends, family and medical professionals and both current and previous symptoms. The characteristics of these illness perceptions then determine what actions or coping strategies the individual may employ with respect to their condition. Once these strategies have been used, the effect of these actions or attitudes is assessed, which can lead to illness perceptions being adjusted. According to the model, therefore, illness perceptions are expected to change over time. In support of
the model, this has been observed in longitudinal studies of different diseases but also in response to programmes designed to manage chronic conditions (208-210).

Initial research into illness perceptions was performed by Leventhal and others using semi-structured interviews. The limitations of being able to generalize this process, however, and the wish to study illness perceptions in populations led to the development of the Illness Perception Questionnaire (IPQ (211)). From the qualitative work of Leventhal and others it emerged that there are five distinct domains of perceptions that exist across individuals. These include the perceived severity of impact that the illness will have on the individual (termed consequences), the likely duration of the illness (timeline; acute/ chronic), the symptoms attributed to it (identity) and perceived causes. A domain of the original instrument that is of great interest with regard to research into treatment effectiveness is the Cure/Control domain which relates to beliefs about whether or not the course or symptoms of the illness may be altered. Factor analysis of studies using the original instrument, however, demonstrated that the questions designed to examine this domain loaded onto two discrete factors. This suggested that two different concepts were in fact...
being measured. Further examinations revealed that the first factor related to beliefs about whether the illness could be modified by actions that the individual could take themselves and the second to beliefs about whether medical treatments were effective in altering the symptoms and course of the illness. This distinction was recognised in the revised version of the instrument (IPQR) (212), in which these different concepts within cure/control were expressed as **personal control** and **treatment control** domains. The treatment control domain of the IPQR, therefore, offers a specific measure of the degree to which an individual believes that the symptoms of their illness are modifiable by medical treatments. Further work has also provided a brief form of the illness perception questionnaire (BIPQ) (213).

Several studies have examined the operation of Illness perceptions in OA in general. A cross-sectional study of 316 patients with lower limb OA (214) demonstrated that subjects with higher scores for the domains consequences and chronic timeline (i.e. those who viewed their illness as severe and unremitting) reported higher levels of disability than might be predicted from a model based on physical factors. Patients with lower scores for the same domains were more likely to report lower levels of disability than predicted. While definitive proof of causation can only be provided by an interventional trial, some evidence for a causal relationship is suggested by longitudinal studies. In such a longitudinal study of 241 patients with OA at various body areas, ‘negative’ illness perceptions at baseline (including less perception of control and higher consequences) were predictive of higher levels of disability at six years than more ‘positive’ baseline illness perceptions (210). This relationship persisted after correction for demographic factors and baseline pain and disability.

Four studies have examined the role of illness perceptions in predicting the outcome of arthroplasty, using a range of instruments.

The first study of illness perceptions in 107 patients following THR showed that higher control perceptions (not divided into treatment control/personal control) predicted better improvements in function at 9 months following surgery, although other domains did not (215). An illustration that illness perceptions are not synonymous with
expectations was provided by this study since patients’ expectations of surgery were not found to predict outcome, although they did predict depression at 9 months. Subsequent investigations have provided further evidence that illness perceptions influence the outcome of surgery. A study using BIPQ confirmed that higher treatment control perceptions predicted better outcomes following THR and that more severe perceived consequences were associated with a poorer outcome (216). By contrast, these factors did not predict the outcome of a similar number of patients post knee replacement, although a higher level of concern about illness (a dimension not found in the other versions of the questionnaire, capturing elements of emotional response and consequences) predicted lower pain reduction (216). Two further studies have examined the predictive value of the IPQR in joint replacement. In a prospective cohort of 130 patients undergoing THR or TKR, high scores for timeline (i.e. perceived illness as more chronic) preoperatively were found to predict persistent pain after 6 months in a multivariable model. Borderline associations were seen between persistent pain and emotional representations domain of the IPQR (p<0.06) (217). By contrast, control perceptions were not found to predict outcome in this study, even in univariate analysis, and consequences was excluded from analysis due to low internal consistency of the scale. In a study of 100 patients undergoing TKR, the IPQR dimensions coherence and consequences were found to explain 7.9% of variance of pain and functional outcome 6 weeks post operatively in addition to 13.5% explained by preoperative symptom scores, but no additional variance at one year (187).

Overall, all studies which have examined illness perceptions as predictors of response to orthopaedic surgery have demonstrated that more negative illness perceptions predict poorer outcomes, although there is variation between studies as to which dimensions constitute the best predictors in each case.

1.5.7 Evidence that change in psychological factors may influence outcome

Identifying determinants of response to intra-articular injection could allow targeting of treatment. However, it might be possible to improve treatment outcomes, were the determinants modifiable. The advantage of many psychological variables in this
context, including illness perceptions, pain catastrophizing and depression is that they are amenable to modification. Demonstration that treatment responses are influenced by psychological factors could, therefore, inform the development or adaptation of existing psychological interventions to improve the outcomes of patients with otherwise poor expectations of treatment.

The dynamic aspect of illness perceptions is explicitly expressed in the Common Sense Model which describes them(218) and their modification by intervention demonstrated in the cases of chronic pain, chronic lung disease, diabetes and heart disease (208;219-221). However, this characteristic is not unique to illness perceptions. That depression and mental health can be improved by intervention needs no elaboration. A large longitudinal study demonstrated that treatment to improve depression also produced improvements in self reported pain and function in patients with osteoarthritis (95).

Several further investigations illustrate associations between changes in psychological parameters and treatment outcomes in the context of knee osteoarthritis.

A quasi-experimental study using an intervention to reduce pain catastrophizing in patients prior to knee replacement surgery suggested both that pain catastrophizing could be reduced by intervention but also that outcomes following knee replacement were superior to those in a cohort who did not receive the intervention (222).

Two further studies demonstrate physical improvements in rehabilitation being mediated by improvements in psychological factors. A study of 357 patients enrolled in a physical training programmes or control showed that improvements in physical performance shown in the treatment groups were fully explained by changes in self efficacy and pain (223). In a further 152 patients with knee OA undergoing an eight week exercise programme, changes in self assessed knee function were explained by changes in fear of activity as well as perceived instability (224).
1.6 Potential role of accuracy of injection as predictor of response.

The observation in one trial of greater pain reduction in patients with effusions (154) has provoked a debate which has focused almost exclusively on the possible role of inflammation in OA and its effects on the response to IACI (152). An alternative hypothesis; that injections might be more effective in patients with effusion because of a higher probability of entering the joint cavity accurately, has received surprisingly little attention in the context of knee arthritis and has not been investigated conclusively. This hypothesis makes the assumptions that the structures causing pain in knee OA are intra-articular, which may not necessarily be true (63). From the point of view of accuracy, while few would now advocate hip injections without recourse to imaging guidance, it is commonly perceived to be unusual for injections to fail to enter the knee joint. However, some studies, using an external validation of accuracy such as joint arthrography, have demonstrated figures as high as 30% (225). A study by Sambrook (161) did examine the possible importance of intra-articular placement on response in comparing injections (assumed to be) given by the intra-articular route with injections of identical composition administered to the patellar margin and found no difference in response. The authors acknowledge, however, that the study lacked power to allow firm conclusions relating to effectiveness. It is known that using US guidance can improve the accuracy of injection (226) but studies employing US guidance have rarely controlled for the potential placebo effect of the US itself. An exception to this is the study by Cunnington et al (227), involving injection of a large variety of inflamed joints in different forms of inflammatory arthritis (as opposed to osteoarthritis), did not demonstrate any difference in pain reduction between injections which entered the joint and those that failed to do so, with injection accuracy in this study being verified using intra-articular contrast injection and post-injection radiographs. Despite this, surprisingly, there are no published studies that have addressed the question of whether accuracy of injection affects treatment outcome in OA and consequently whether improving accuracy of injections given in knee OA could improve outcomes.

Determination of the accuracy of knee injections guided by clinical examination in previous studies has employed intra-articular radiographic contrast injection
Air arthrosonography provides an alternative potential method of ascertaining the accuracy of injection that does not involve additional radiographs and is potentially more widely applicable in a clinical setting (229). Since atmospheric air is readily visible on US, it can be used as a contrast medium when added to injected material that can allow intra-articular injection to be verified. The technique has been described in the role of verifying injections placed under direct ultrasound guidance (229). It could, however, be used to determine whether injections given by clinical examination were delivered to the intra-articular space by the addition of a small volume of air to the injection.

1.7 Summary and outline of project.

Knee osteoarthritis is a common problem with increasing prevalence. It has major direct and indirect costs for the health and social economy, particularly including the costs of joint replacement surgeries. Since no disease modifying drugs are currently available that can alter the course of the disease, currently available treatments for the condition aims to reduce symptoms. Intra-articular steroid injections have been shown to be effective in the short term in placebo-controlled trials. The variation in the reported degree of response to treatment observed, both anecdotaly and experimentally, is large. Understanding the causes for this variation would allow intra-articular corticosteroid injections to be targeted in an efficient manner and their potential role in treatment better understood. Review of the existing literature produced no strong evidence in support of any potential predictor of response studied. Putative predictors were almost exclusively physical or disease related and where individual studies suggested positive findings, others reached opposing conclusions. At the time of writing there had been no attempts at conducting a systematic review of this literature.

Absent from previous studies also is any significant attempt to explore the role of psychological factors or the effect of accuracy of injection. Accuracy of injection is assumed by patients and clinicians alike to influence outcome but this assumption has not been tested adequately, particularly in the case of OA. Psychological factors have
been shown to influence pain reporting in knee OA and there is reliable evidence that they influence outcomes following orthopaedic surgery. There are also data, although fewer, supporting a role in predicting the outcome of non-surgical treatments for OA.

The broad aim of this thesis therefore was to investigate the effects of accuracy of injection and of selected psychological factors on the outcome of intra-articular corticosteroid injections in knee osteoarthritis.

The psychological factors that were selected for study were illness perceptions, pain catastrophizing and depression. Illness perceptions are an attractive area for study for several reasons: they are supported as important determinants of health outcomes by a growing body of literature in OA as well as other chronic conditions (230;231). The instruments capture several elements within one established psychological framework; several domains show significant correlation with other potentially important concepts such as self efficacy (232) and some similarities with treatment expectations. Pain catastrophizing, while a theoretically more problematic construct, has well demonstrated associations both with pain and with outcomes in arthroplasty studies. It may be measured with validated questionnaires. Furthermore it has been demonstrated that interventions to modify pain catastrophizing are successful and lead to changes in health outcomes. As discussed, depression is closely correlated with pain catastrophizing and it would be difficult not to study depression in conjunction with pain catastrophizing. Depression is a widely understood and recognised clinical concept, has been shown to be associated with outcomes in arthroplasty and is known to be modifiable by both pharmacological and psychological interventions.

In view of the inconclusive evidence from previous studies, selected physical factors were re-examined in the context of this prospective study, together with the first systematic large scale examination of the effect of accuracy of injection on outcome, and the ability of these variables to predict response to treatment was compared with that of the selected psychological factors.
2.1 Aims and objectives

The overall aim of the study was to identify specific factors that may determine the degree of pain relief reported by patients following an open label injection of corticosteroid and local anaesthetic in patients with symptomatic knee OA.

Within the objectives section, ‘treatment’ refers to intra-articular corticosteroid injection and ‘response’ refers to clinically significant reduction in reported symptoms of knee osteoarthritis at three and nine weeks post treatment, as defined by the outcome measures described in the methods section.

Objectives:

1. Conduct a systematic review of previous studies seeking to determine predictors of response to intra-articular corticosteroid injection in knee OA.

2. Conduct an observational study of IACI in knee OA, concentrating on potential predictors suggested by the literature review and specifically aiming to:
   a. Investigate the relationship between reported levels of baseline illness perceptions (in particular treatment control perceptions) and rates of response to treatment.
   b. Investigate the relationship between levels of pain catastrophizing reported at baseline and rates of response to treatment.
   c. Investigate the relationship between levels of depression reported at baseline and rates of response to treatment.
   d. Investigate the potential of physical factors including ultrasonographic markers of inflammation, radiographic severity and accuracy of injection, as indicated by ultrasound method to predict response to treatment.
Chapter Three:

Intra-articular corticosteroid injection in osteoarthritis of the knee and hip: factors predicting pain relief - a systematic review

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Intra-articular Corticosteroid Injection in Osteoarthritis of the Knee and Hip: Factors Predicting Pain Relief—A Systematic Review

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Objectives: Variations in the degree of pain relief reported by patients with osteoarthritis following intra-articular corticosteroid injections are well recognized but the reasons for this are not widely understood and factors which might predict variations in response have not been subjected to systematic review. We set out to review systematically the literature relating to predictors of pain reduction following intra-articular corticosteroid injections in patients with knee and hip osteoarthritis.

Methods: Searches were performed using Medline, EMBASE, Web of Knowledge and MeSH search of Pubmed, the last search being performed in August 2012. Search terms included knee osteoarthritis, hip osteoarthritis, corticosteroid and related terms, and intra-articular injection. Papers were selected and reviewed by 2 reviewers. For inclusion, papers were required to describe studies in which patients with osteoarthritis of the knee or hip received intra-articular corticosteroid injection as an intervention, contain clearly defined outcome measures relating to pain and contain analysis relating to predictors of clinical response to treatment.

Results: Twenty-one studies met criteria for inclusion from a total of 54 papers reviewed in full. Eight of these related to hip OA and 13 related to knee OA. No factors that were investigated as potential predictors of response, including radiographic grade and clinical or sonographic evidence of inflammation or synovial hypertrophy were supported by strong evidence. The review also identified that several plausible potential predictors had not been studied to date.

Conclusions: Previous research has not identified reliable predictors of response to IA corticosteroid injections, a widely practised intervention in knee and hip OA. Further studies are required if this question is to be answered.

Editorial observation: Osteoarthritis (OA) is the fourth most common cause of years lost to disability in the world according to WHO estimates [1]. Osteoarthritis of the knee and hip, which have a prevalence of over 29% and 7% in those over 65, respectively [2,3], are responsible for a significant proportion of this disability, much of which can be attributed to pain. In the absence of licensed disease-modifying treatments for OA [4], intra-articular (IA) corticosteroid injections are commonly used for pain relief in primary and secondary care. In knee OA, their short term (up to 3 weeks) efficacy has been confirmed in systematic reviews of placebo-controlled trials [5], with some pooled trial data suggesting a possible benefit of up to 24 weeks [6]. Responses vary greatly between patients, both in duration and magnitude. However, apart from the frequently cited role of effusion in knee OA [10,11,17,18,35], little is known about the determinants of this variability.
This means that IA corticosteroid injections are presently administered without the ability to predict who would receive most or least pain relief from this common intervention, and this has implications both for individual patients and for resource utilization. We conducted a systematic review of published evidence in order to determine what is known about the factors predicting pain reduction following IA corticosteroid injections in knee and hip OA.

METHODS

We searched Medline, Embase, and Web of Science using the terms “knee joint” and “hip joint”, “osteoarthritis”, “osteoarthrosis”, “knee osteoarthritis”, “hip osteoarthritis”, “intra-articular injections”, “steroids”, and “adrenal cortex hormones”. MeSH terms (knee joint, hip joint, osteoarthritis, osteoarthrosis, knee, osteoarthritis; hip, injections; intra-articular, corticosteroid, adrenal cortex hormones, intra-articular corticosteroid) were also used to search PubMed. Abstracts of both randomized controlled trials and observational studies that included IA corticosteroid injections in patients with knee or hip osteoarthritis were examined and the full paper retrieved for review. Reference lists from papers included were examined for further suitable articles. We included observational studies since they frequently contain a higher number of patients. Manuscripts published in English language were included in the review, if, they described studies in human adults with osteoarthritis of the knee or hip joint, reported IA corticosteroid injections as study intervention, stated defined outcome measures relating to pain, and contained evidence of statistical analysis attempting to identify factors associated with clinical response to treatment. Jadad scores were calculated where applicable (see Table 1).

Search strategy: (1) Knee osteoarthritis; (2) hip osteoarthritis; (3) knee osteoarthrosis; (4) hip osteoarthrosis; (5) osteoarthritis; (6) Osteoarthrosis; (7) knee joint; (8) hip joint; (9) #7 OR #8; (10) #5 OR #6; (11) #10 AND #9; (12) #1 OR #2 OR #3 OR #4 OR #11; (13) Corticosteroid*; (14) Steroid; (15) Adrenal cortex hormones; (16) glucocorticoid; (17) triamcinolone; (18) methylprednisolone; (19) intra-articular injection; and (20) #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19; (21) #12 AND #20.

RESULTS

The search, last performed in August 2012, identified 156 articles suitable for review (Medline: 40; EMBASE: 37; MeSH: 37; Web of Science: 42). No additional articles were identified from reference lists. Removal of 92 duplicated records, 7 conference abstracts, and 3 non-English language studies left 54 papers meeting criteria for further review. These were studied in full and a total of 21 met the criteria for inclusion (Fig. 1): 13 described studies of knee OA and 8 described studies of hip OA (Table 1).

A single study containing appropriate analysis was excluded because all patients received joint lavage in addition to IA corticosteroid injections [7]. Two studies of knee OA that compared different steroid preparations [8,9] were included since currently a variety of steroid preparations are used clinically and this may be a factor influencing response.

KNEE (SEE TABLE 2)

Clinical and Structural Joint Factors

Five studies [10–15], of which 3 [10,13,14] were placebo-controlled trials, examined the influence of joint effusion on reduction of pain following injection. One placebo-controlled trial [10] demonstrated significantly greater pain reduction at 1 week in those patients in whom fluid was aspirated at the time of injection (P < 0.01) and in those with clinical evidence of effusion (P < 0.05). However, 2 other placebo-controlled trials found no relationship between effusion and response: in 20 patients 1 week after treatment with 20 mg triamcinolone hexacetonide [14] and in 59 patients 3 weeks after treatment with 40 mg methylprednisolone acetate [13].

A study comparing 75 patients receiving 40 mg methylprednisolone acetate with 71 receiving tidal irrigation found no difference in pain within the steroid group at 1 week but greater reduction at 26 weeks in those patients with clinical effusion than those without effusion (P = 0.04) [11]. A study of 57 subjects, in which knee effusion was an inclusion criterion, reported no difference in pain relief between groups with larger and smaller effusions at 3 weeks, using a non-validated clinical effusion grade; however, there was a trend (P = 0.07) towards greater pain reduction after 8 weeks in patients with smaller effusions than in those with larger effusions [12].

One observational study of 86 patients reported greater reduction of night pain (assessed by VAS) at 1 and 6 weeks in patients with increased skin temperature, as determined during knee examination (P < 0.05) [15], whereas a crossover placebo-controlled trial of 59 patients found no relationship between skin temperature and response at 3 weeks [13].

Two studies examined joint tenderness. One placebo-controlled trial found the presence of local tenderness to be associated with responder status, defined as 15% reduction in pain VAS at 3 weeks by crude odds ratios (OR 1.80 [CI 1.03,1.67]), but did not find it to be a significant predictor of response in logistic regression analysis [13]. One observational study states that tenderness was addressed as a potential predictor, but did not state that an association with response was detected [15].

Two studies of knee OA examined high resolution ultrasound (US) findings as potential predictors of response. An observational study [15] of 86 patients used
definitions from a EULAR survey of OA [16] to define the presence or the absence of sonographic joint effusion and synovial hypertrophy (see Appendix). It found no relationship between either parameter and clinical response. A placebo-controlled trial including 31 patients receiving IA corticosteroid injections defined “inflammatory disease” as sonographic synovial hypertrophy > 5 mm, with or without sonographic effusion [17]. No difference in pain reduction was present at 4 weeks, but at 12 weeks those with no features of inflammation at baseline had lower pain scores than those who had features of inflammation ($P = 0.03$), implying a longer duration of treatment effect in patients without sonographic inflammation. This was also the only study we found to have examined serum biomarkers including IL1β, TNFα, IL6, Matrix metallo-proteinase 1 (MMP1), and CRP as potential predictors of sonographic inflammation and/or clinical response—no significant associations were found. Two studies examining synovial fluid white-cell count also did not find any relationship with response [10,18]. We did not identify any studies examining other synovial fluid biomarkers (e.g. MMP1, IL1β, and TNFα) as potential predictors of response.

Five studies investigated the relationship between baseline radiographs and response to injection [10,11,18,18–20]. One observational study, using the Kellgren & Lawrence grading system (KL) and including 79 patients with grade 0–4 disease, demonstrated greater improvements in pain from baseline at 26 weeks in those patients with milder (grade 0–1) radiographic changes compared with severe (3–4) changes ($P = 0.019$) [11]. No interaction between KL grade (limited to grades 2 and 3) and response was found in a placebo-controlled trial of

**Figure 1 Flow-chart of literature search.**
<table>
<thead>
<tr>
<th>Author</th>
<th>Design, Total Numbers; Comparators (Number Receiving Intervention)</th>
<th>Numbers Receiving IACI</th>
<th>Follow-up (Weeks)</th>
<th>Primary Outcome</th>
<th>Definition of Response</th>
<th>Secondary Outcome</th>
<th>Jadad Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee</td>
<td>Valtonen [8] Single blind comparison in 42 patients with knee OA “with evidence of inflammation”; 20 mg THA (21) and 6 mg BM (21).</td>
<td>42</td>
<td>1, 2, 4</td>
<td>Pain likert</td>
<td>Not defined</td>
<td>Patients requesting reinjection</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Wright et al. [9] Double blind crossover study, 38 joints in 25 patients with knee OA; course of 4 x IA injections placebo (38), 25 mg HC acetate (38) and 25 mg HC tertiary-butyl-acetate (38). Injections separated by 8 weeks.</td>
<td>38 joints × 2 as crossover (76)</td>
<td>2, 4, 6, 8</td>
<td>Patient pain likert 0–4, physician assessed tenderness (0–4)</td>
<td>Improved/not</td>
<td>Range of movement, 50 m walk time</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Gaffney et al. [10] Double blind comparison in 84 patients with knee OA (clinical and radiographic); 20 mg THA (42) vs placebo (42).</td>
<td>42</td>
<td>1, 6</td>
<td>Pain VAS</td>
<td>Not defined</td>
<td>Patients reporting improvement</td>
<td>3</td>
</tr>
<tr>
<td>Arden [11]</td>
<td>Single blind comparison in 150 patients with knee OA (clinical diagnosis, KL 0–4); 40 mg MPA (79) vs tidal irrigation (71).</td>
<td>79</td>
<td>2, 4, 12, 26</td>
<td>WOMAC pain subscale</td>
<td>Not defined</td>
<td>WOMAC function, WOMAC stiffness, patient-reported improvement</td>
<td>4</td>
</tr>
<tr>
<td>Pyne et al. [12]</td>
<td>Doubleblind comparison of in 57 patients with knee OA with effusion (ACR, KL &gt; 1); 20 mg THA (29) and 40 mg MPA (28).</td>
<td>57</td>
<td>3, 8</td>
<td>Pain VAS</td>
<td>Not defined</td>
<td>Lequesne, stair climbing time</td>
<td>4</td>
</tr>
<tr>
<td>Jones and Doherty [13]</td>
<td>Double blind crossover comparing 59 patients with knee OA (ACR, painful); MPA 40 mg (59) with placebo (59). Injections separated by 8 weeks.</td>
<td>59 patients as crossover (118)</td>
<td>3, 8</td>
<td>Pain VAS</td>
<td>15% improvement in Pain VAS</td>
<td>n/a</td>
<td>4</td>
</tr>
<tr>
<td>Study Reference</td>
<td>Study Design</td>
<td>Participants</td>
<td>Intervention 1</td>
<td>Intervention 2</td>
<td>Study Outcomes 1</td>
<td>Study Outcomes 2</td>
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</tr>
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<tr>
<td>Friedman and Moore [14]</td>
<td>Double blind comparison in 34 patients with knee OA with “no signs of inflammation”; THA 20 mg (17) with placebo (17).</td>
<td>17</td>
<td>1, 4</td>
<td>Pain likert</td>
<td>Not defined</td>
<td>n/a</td>
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<tr>
<td>Pendleton et al. [15]</td>
<td>Open-label study of 86 patients with knee OA (ACR); MPA 40 mg (86).</td>
<td>86</td>
<td>1, 6</td>
<td>WOMAC pain scale</td>
<td>20% and 50% improvement in WOMAC</td>
<td>VAS for night pain</td>
<td>n/a</td>
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<tr>
<td>Chao et al. [17]</td>
<td>Double blind comparison in 61 patients with knee OA (ACR); 40 mg TA (31) vs placebo (30).</td>
<td>31</td>
<td>4, 12</td>
<td>WOMAC pain subscale</td>
<td>Not defined</td>
<td>Physician Global Assessment</td>
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<tr>
<td>Dieppe et al. [18]</td>
<td>Paper describing 2 double blind RCTs: trial A 12 patients with bilateral knee OA, trial B 16 patients, 24 knees with effusion with crossover at 1/52; THA 20 mg (24) vs placebo (24).</td>
<td>36 joints, 24 as crossover (60)</td>
<td>1, 2, 4, 6</td>
<td>Pain VAS</td>
<td>Not defined</td>
<td>Blinded patient treatment preference</td>
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<tr>
<td>Raynauld et al. [19]</td>
<td>Double blind comparison in 68 patients with knee OA (ACR, KL 2 or 3); 40 mg TA (34) with placebo (34). Injections every 12 weeks for 2 years.</td>
<td>34</td>
<td>Every 12 for 2 years</td>
<td>WOMAC pain subscale</td>
<td>Not defined</td>
<td>Radiographic change, WOMAC total, Physician Global Assessment, Patient Global Assessment, range of movement, 50 m walk time</td>
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<tr>
<td>Leopold et al. [20]</td>
<td>Double blind comparison in 100 patients with knee OA (radiographic, painful); 3 × injections HA (50) vs 1 × betamethasone plus 2 × placebo injections (50).</td>
<td>50</td>
<td>12, 26</td>
<td>WOMAC, total</td>
<td>Not defined</td>
<td>Pain VAS, Knee Society rating scale</td>
<td>3</td>
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<tr>
<td>Sambrook et al. [21]</td>
<td>Double blind comparison in 38 patients with knee OA (radiographic, painful); 80 mg MPA IA (19) vs 80 mg MPA peripatellar (19).</td>
<td>38 (19 as IACI)</td>
<td>1, 4, 12</td>
<td>Pain VAS</td>
<td>Not defined</td>
<td>Pain VAS (worst, least, rising, passive movement), tenderness [1–8], 25 m walk time, 25 m walk pain</td>
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</tr>
<tr>
<td>Author</td>
<td>Design, Total Numbers; Comparators (Number Receiving Intervention)</td>
<td>Numbers Receiving IACI</td>
<td>Follow-up (Weeks)</td>
<td>Primary Outcome</td>
<td>Definition of Response</td>
<td>Secondary Outcome</td>
<td>Jadad Score</td>
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<tr>
<td>Lambert et al. [22]</td>
<td>Double blind comparison in 52 patients with hip OA (primary OA, ACR, &gt; 40 years, symptoms &gt; 6 months, WOMAC score &gt; 40 mm on each subscale); 40 mg THA (31) or placebo (21).</td>
<td>31</td>
<td>4, 8, 12, 26</td>
<td>WOMAC pain subscale</td>
<td>20% improvement in WOMAC</td>
<td>Womac 50% improvement pain, WOMAC function, WOMAC stiffness, pain vas, SF36, range of movement</td>
<td>5</td>
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<tr>
<td>Plant et al. [23]</td>
<td>Open-label study in 45 patients with radiographic changes in hip (27 OA, 15 RA, 3 AS); 80 mg MPA (45).</td>
<td>45 (27 OA)</td>
<td>2, 12, 26</td>
<td>Pain VAS</td>
<td>Not defined</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Flanagan et al. [24]</td>
<td>Double blind comparison in 35 patients on waiting list for hip replacement; 20 mg THA and bupivacaine (12) or bupivacaine (12), placebo (12).</td>
<td>12</td>
<td>1, 2, 3, 4</td>
<td>Pain likert (total change)</td>
<td>Not defined</td>
<td>1–5 likert for activity, stability, movement</td>
<td>4</td>
</tr>
<tr>
<td>Deshmukh et al. [25]</td>
<td>Retrospective analysis of assessor-blinded response to 80 mg IA MPA in 217 patients with hip OA (clinical diagnosis, KL 0–4)</td>
<td>217</td>
<td>Immediate, 2</td>
<td>Pain improvement VAS</td>
<td>50 mm score on pain improvement VAS</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Young et al. [26]</td>
<td>Double blind RCT of 110 patients with hip OA (clinical diagnosis); 40 mg TA in 2 ml bupivacaine (55) or 40 mg TA in 2 ml bupivacaine and 6 ml saline (55).</td>
<td>110</td>
<td>Every 2 weeks for 12</td>
<td>WOMAC OARSI response, effect size</td>
<td>Oxford Pain Chart</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Atchia et al. [27]</td>
<td>Single blind comparison in 77 patients with hip OA (ACR criteria, moderate to severe); 120 mg MPA (19) with HA (19), saline (19) or no intervention (20).</td>
<td>19</td>
<td>1, 4, 8</td>
<td>Numerical rating scale for pain (total change)</td>
<td>OARSI response</td>
<td>WOMAC pain, WOMAC function, OARSI response, Patient Global Assessment.</td>
<td>3</td>
</tr>
</tbody>
</table>
68 patients receiving repeated injections over 2 years [19]. Three studies used other grading systems [10,18,20], 2 of which do not state if and how the grading system was validated [18,20]. None of these found any association between radiographic grade and response at time-points between 1 week and 6 months.

**General Patient Characteristics**

*Age and body-mass index (BMI)* have been found to be not associated with response at any time point in 2 separate studies [11,19]. A single trial comparing betamethasone with hyaluronic acid in 100 patients found significant reductions in pain at 3 and 6 months in male, but not female, patients randomized to steroid [20]. No interaction between *gender* and response was found in a placebo-controlled trial of repeated injections of triamcinolone acetonide in 68 patients over 2 years [19].

One observational study found that *greater baseline pain* was associated with greater reduction of pain at 1 and 6 weeks (*P = 0.01*) [13], whereas a placebo-controlled trial did not demonstrate such an association [10], nor did it find any association between response and baseline HAQ score. Duration of symptoms was investigated in 3 studies [10,11,19] (2 placebo-controlled) and not found to be associated with response.

**Psychological Factors**

Only one study [13] examined the relationship of clinical response (at 3 weeks) with psychological factors (anxiety and depression using the Hospital Anxiety and Depression Scale; HADS)—no association was found.

**Factors Related to the Injection**

One study [21] used a blinded design to compare injections of methylprednisolone and xylocaine administered intra-articularly with injections to the patellar margin in 38 patients with knee OA. No significant difference in pain relief between groups was observed at 1 week, 1 month or 3 months.

Three trials included comparisons of *different corticosteroid preparations* in knee OA. Two studies compared triamcinolone hexacetonide with betamethasone [8] and methylprednisolone [12]. Triamcinolone caused significantly greater pain reduction than methylprednisolone at 3 but not 8 weeks [12]. An earlier study demonstrated superiority of triamcinolone hexacetonide over betamethasone at 1 week but not 2 or 4 weeks [8]. One comparing hydrocortisone tertiary-butylic-acetate with hydrocortisone acetate showed superiority over placebo at 2 weeks only for the former, but direct comparison of the 2 drugs showed no statistical difference [9].

**HIP (SEE TABLE 3)**

All 8 studies included in this systematic review were performed using image-guidance; 5 fluoroscopic [22–26].

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Pain VAS</th>
<th>Other Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olesz et al. [28]</td>
<td>101 patients with hip OA (ACR, radiographic OA)</td>
<td>40 mg MPA (32) or saline (34)</td>
<td>120</td>
<td>2, 4, 12 Pain VAS; walking (total change)</td>
<td>WOMAC, improve in WOMAC</td>
</tr>
<tr>
<td>Robinson et al. [29]</td>
<td>120 patients with hip OA (clinical diagnosis)</td>
<td>40 mg MPA (75) 80 mg MPA (45)</td>
<td>120</td>
<td>6, 12</td>
<td>WOMAC</td>
</tr>
</tbody>
</table>

Abbreviations: ACR, American College of Rheumatology; THA, triamcinolone hexacetonide; RA, rheumatoid arthritis; AS, ankylosing spondylitis; MP, methylprednisolone acetate; HA, hyaluronic acid; IA, intra-articular; HC, hydrocortisone; KCL, Kellgren–Lawrence; VAS, visual analog scale; HAQ, health assessment questionnaire; HAD, hospital anxiety and depression scale; ns, non-significant; BMI, body-mass index; n/a, not applicable.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Author</th>
<th>Number Receiving IA Steroid</th>
<th>Method of Measurement</th>
<th>Outcome Measure</th>
<th>Observation Point (Weeks)</th>
<th>Result</th>
<th>Method of Analysis</th>
<th>Jadad Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical and structural joint factors</strong></td>
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</tr>
<tr>
<td>Effusion</td>
<td>Gaffney et al. [10]</td>
<td>42</td>
<td>Clinical examination (present/absent)</td>
<td>Pain VAS (absolute change)</td>
<td>1, 6</td>
<td></td>
<td>1 week: greater pain reduction in patients with effusion ($P &lt; 0.05$). 6 weeks: ns</td>
<td>3</td>
</tr>
<tr>
<td>Effusion</td>
<td>Gaffney et al. [10]</td>
<td>42</td>
<td>Fluid aspirated (yes/no)</td>
<td>Pain VAS (absolute change)</td>
<td>1, 6</td>
<td></td>
<td>1 week: fluid aspirated significantly greater pain reduction ($P &lt; 0.01$). 6 weeks: ns</td>
<td>3</td>
</tr>
<tr>
<td>Effusion</td>
<td>Pyne et al. [12]</td>
<td>57</td>
<td>Clinical effusion grade (non-validated)—all patients had effusion</td>
<td>Pain VAS (absolute change)</td>
<td>3, 8</td>
<td></td>
<td>8 weeks: trend ($P = 0.07$) towards greater pain reduction in THA group where grade 1 effusion vs grade 2–3. Ns THA week 1, ns MPA week 1 and 8</td>
<td>4</td>
</tr>
<tr>
<td>Effusion</td>
<td>Arden [11]</td>
<td>79</td>
<td>Clinical Examination (present/absent)</td>
<td>WOMAC pain subscale (absolute change)</td>
<td>2, 4, 12, 26</td>
<td></td>
<td>26 weeks: significantly greater pain reduction in patients with baseline effusion ($P = 0.04$)</td>
<td>4</td>
</tr>
<tr>
<td>Effusion</td>
<td>Jones and Doherty [13]</td>
<td>59</td>
<td>Clinical Examination (present/absent)</td>
<td>Pain VAS response (15% improvement)</td>
<td>3</td>
<td>ns</td>
<td>Stepwise logistic regression</td>
<td>4</td>
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<tr>
<td>Effusion</td>
<td>Jones and Doherty [13]</td>
<td>59</td>
<td>Fluid aspirated (yes/no)</td>
<td>Pain VAS response (15% improvement)</td>
<td>3</td>
<td>ns</td>
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<tr>
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<td>17</td>
<td>Fluid aspirated (yes/no)</td>
<td>Pain likert (absolute change)</td>
<td>1, 4, 8</td>
<td>ns</td>
<td>Univariate analysis</td>
<td>4</td>
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<tr>
<td>Parameter</td>
<td>Study</td>
<td>N</td>
<td>Methodology</td>
<td>Outcome Measure</td>
<td>Effect Size</td>
<td>Significance</td>
<td>Notes</td>
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<tr>
<td>Skin temperature</td>
<td>Pendleton et al. [13]</td>
<td>86</td>
<td>Clinical examination</td>
<td>Pain VAS (night pain, percentage change)</td>
<td>1, 6</td>
<td>1 week: 39% greater reduction in night pain where increased warmth present (P &lt; 0.05)</td>
<td>Not stated n/a</td>
<td></td>
</tr>
<tr>
<td>Local tenderness</td>
<td>Gaffney et al. [10]</td>
<td>42</td>
<td>Clinical examination</td>
<td>Pain VAS (absolute change)</td>
<td>1, 6</td>
<td>ns</td>
<td>Logistic regression 3</td>
<td></td>
</tr>
<tr>
<td>Local tenderness</td>
<td>Jones and Doherty [13]</td>
<td>59</td>
<td>Clinical examination</td>
<td>Pain VAS response (15% improvement)</td>
<td>3</td>
<td>3 weeks: patients with local tenderness OR 1.80 [1.03,1.67] of response (ns in logistic regression)</td>
<td>Univariate as crude OR vs responder status</td>
<td></td>
</tr>
<tr>
<td>US synovitis</td>
<td>Chao et al. [17]</td>
<td>31</td>
<td>US synovitis (&gt;5 mm; yes/no)</td>
<td>WOMAC pain subscale (absolute change)</td>
<td>4, 12</td>
<td>12 weeks: greater reductions in pain in synovitis-negative patients at 12 weeks (P = 0.03) 4 weeks: ns</td>
<td>Linear regression model 4</td>
<td></td>
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<tr>
<td>US synovitis</td>
<td>Pendleton et al. [15]</td>
<td>86</td>
<td>US effusion (yes/no, as per EULAR definition)</td>
<td>WOMAC pain (percentage change)</td>
<td>1, 6</td>
<td>ns</td>
<td>Not stated n/a</td>
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<tr>
<td>US effusion</td>
<td>Chao et al. [17]</td>
<td>31</td>
<td>US effusion (present/absent)</td>
<td>WOMAC pain subscale (absolute change)</td>
<td>4, 12</td>
<td>ns</td>
<td>Linear regression model 4</td>
<td></td>
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<tr>
<td>US effusion</td>
<td>Pendleton et al. [15]</td>
<td>86</td>
<td>US synovitis (yes/no, as per EULAR definition)</td>
<td>WOMAC pain (percentage change)</td>
<td>1, 6</td>
<td>ns</td>
<td>Not stated n/a</td>
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<tr>
<td>Biomarkers</td>
<td>Chao et al. [17]</td>
<td>31</td>
<td>Various</td>
<td>WOMAC pain subscale (absolute change)</td>
<td>4, 12</td>
<td>ns</td>
<td>Logistic regression analysis 4</td>
<td></td>
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<tr>
<td>Synovial Fluid WCC</td>
<td>Dieppe et al. [18]</td>
<td>36</td>
<td>Microscopy</td>
<td>Pain VAS (absolute change)</td>
<td>ns</td>
<td>Correlation (Pearson’s r)</td>
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<tr>
<td>Synovial Fluid WCC</td>
<td>Gaffney et al. [10]</td>
<td>42</td>
<td>Microscopy</td>
<td>Pain VAS (absolute change)</td>
<td>1, 6</td>
<td>ns</td>
<td>Logistic regression 3</td>
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<td>Outcome Measure</td>
<td>Observation Point (Weeks)</td>
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<tr>
<td>Radiographic grade</td>
<td>Leopold et al. [20]</td>
<td>50</td>
<td>Mild/moderate/severe (non-validated)</td>
<td>Pain VAS (absolute change)</td>
<td>12, 26</td>
<td>ns</td>
<td>Univariate analysis (Friedman test)</td>
<td>3</td>
</tr>
<tr>
<td>Radiographic grade</td>
<td>Gaffney et al. [10]</td>
<td>42</td>
<td>Global score 1–9 for whole knee</td>
<td>Pain VAS (absolute change)</td>
<td>1, 6</td>
<td>ns</td>
<td>Linear regression analysis (simple regression)</td>
<td>3</td>
</tr>
<tr>
<td>Radiographic grade</td>
<td>Dieppe et al. [18]</td>
<td>36 joints, 24 as crossover (60)</td>
<td>Mild/moderate/severe (non-validated)</td>
<td>Pain VAS (absolute change)</td>
<td>1, 2, 4, 6</td>
<td>ns</td>
<td>Correlation (Pearson’s r)</td>
<td>2</td>
</tr>
<tr>
<td>Radiographic grade</td>
<td>Arden [11]</td>
<td>79</td>
<td>KL grade</td>
<td>WOMAC pain subscale (absolute change)</td>
<td>2, 4, 12, 26</td>
<td>26 weeks: greater improvement in pain in KL 0–1 than 3–4 ($P = 0.012$)</td>
<td>Regression techniques</td>
<td>4</td>
</tr>
<tr>
<td>Radiographic grade</td>
<td>Raynauld et al. [19]</td>
<td>34</td>
<td>KL grade (2 or 3 only)</td>
<td>WOMAC pain subscale, pain VAS</td>
<td>Every 12 weeks over 2 years</td>
<td>ns</td>
<td>Not stated</td>
<td>4</td>
</tr>
</tbody>
</table>

**General patient characteristics**

<p>| Age                        | Raynauld et al. [19]        | 34                         | Standard              | WOMAC pain subscale (absolute change) | Every 12 weeks over 2 years | ns     | Not clear                               | 4           |
| Age                        | Arden [11]                  | 79                         | Standard              | WOMAC pain subscale (absolute change) | 2, 4, 12, 26               | ns     | Regression techniques                    | 4           |
| BMI                        | Arden [11]                  | 79                         | Standard              | WOMAC pain subscale (absolute change) | 2, 4, 12, 26               | ns     | Regression techniques                    | 4           |
| BMI                        | Raynauld et al. [19]        | 34                         | Standard              | WOMAC pain subscale (absolute change) | Every 12 weeks over 2 years | ns     | Not clear                               | 4           |
| Gender                     | Raynauld et al. [19]        | 34                         | Standard              | WOMAC pain subscale (absolute change) | Every 12 weeks over 2 years | ns     | Unclear                                 | 4           |</p>
<table>
<thead>
<tr>
<th>Gender</th>
<th>Leopold et al. [20]</th>
<th>50</th>
<th>Standard</th>
<th>Pain VAS (absolute change)</th>
<th>26</th>
<th>26 weeks: significant improvement in male but not female patients ($P &lt; 0.01$)</th>
<th>Univariate analysis (Friedman test)</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Pain</td>
<td>Pendleton et al. [15]</td>
<td>86</td>
<td>WOMAC pain subscale</td>
<td>WOMAC pain (percentage change)</td>
<td>1, 6</td>
<td>Greater reduction of pain in those with higher baseline WOMAC ($P &lt; 0.01$) but details of analysis not described.</td>
<td>Not described</td>
<td>n/a</td>
</tr>
<tr>
<td>Baseline Pain</td>
<td>Gaffney et al. [10]</td>
<td>42</td>
<td>Pain VAS</td>
<td>Pain VAS (absolute change)</td>
<td>1, 6</td>
<td>ns</td>
<td>Linear regression analysis (simple regression)</td>
<td>3</td>
</tr>
<tr>
<td>Baseline Pain</td>
<td>Raynauld et al. [19]</td>
<td>34</td>
<td>WOMAC pain subscale</td>
<td>WOMAC pain subscale (absolute change)</td>
<td>Every 12 weeks over 2 years</td>
<td>ns</td>
<td>Not clear</td>
<td>4</td>
</tr>
<tr>
<td>Baseline Pain</td>
<td>Arden [11]</td>
<td>79</td>
<td>WOMAC pain subscale</td>
<td>WOMAC pain subscale (absolute change)</td>
<td>2, 4, 12, 26</td>
<td>ns</td>
<td>Regression techniques</td>
<td>4</td>
</tr>
<tr>
<td>Baseline disability</td>
<td>Gaffney et al. [10]</td>
<td>42</td>
<td>Questionnaire (HAQ)</td>
<td>Pain VAS (absolute change)</td>
<td>1, 6</td>
<td>ns</td>
<td>Linear regression analysis (simple regression)</td>
<td>3</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>Gaffney et al. [10]</td>
<td>42</td>
<td>Standard</td>
<td>Pain VAS (absolute change)</td>
<td>1, 6</td>
<td>ns</td>
<td>Logistic regression analysis</td>
<td>3</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>Raynauld et al. [19]</td>
<td>Standard</td>
<td>WOMAC pain subscale (absolute change)</td>
<td>Every 12 weeks over 2 years</td>
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<td></td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>Arden [11]</td>
<td>79</td>
<td>Standard</td>
<td>WOMAC pain subscale (absolute change)</td>
<td>2, 4, 12, 26</td>
<td>ns</td>
<td>Regression techniques</td>
<td>4</td>
</tr>
<tr>
<td>Anxiety and depression</td>
<td>Jones and Doherty [13]</td>
<td>59 as crossover (118)</td>
<td>Questionnaire (HAD)</td>
<td>Pain VAS response (15% improvement)</td>
<td>3</td>
<td>ns</td>
<td>Odds ratios, logistic regression</td>
<td>4</td>
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<tr>
<td>Variable</td>
<td>Author</td>
<td>Number Receiving IA Steroid</td>
<td>Method of Measurement</td>
<td>Outcome Measure</td>
<td>Observation Point (Weeks)</td>
<td>Result</td>
<td>Method of Analysis</td>
<td>Jadad Score</td>
</tr>
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<td>Characteristics of injection</td>
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<td>Route of steroid administration</td>
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<tr>
<td>Steroid preparation</td>
<td>Sambrook et al. [21]</td>
<td>19</td>
<td>Intra-articular vs peripatellar</td>
<td>Pain VAS (absolute change)</td>
<td>1, 3, 12</td>
<td>ns</td>
<td>Univariate analysis (ANOVA)</td>
<td>4</td>
</tr>
<tr>
<td>Steroid preparation</td>
<td>Pyne et al. [12]</td>
<td>57</td>
<td>THA vs MPA</td>
<td>Pain VAS</td>
<td>3, 8</td>
<td>3 weeks: THA greater pain reduction than MPA ($P &lt; 0.01$), 8 weeks: ns</td>
<td>Univariate analysis (ANOVA)</td>
<td>4</td>
</tr>
<tr>
<td>Steroid preparation</td>
<td>Valtonen [8]</td>
<td>42</td>
<td>THA vs BM</td>
<td>Pain likert (absolute change)</td>
<td>1, 2, 4</td>
<td>1 week: THA greater reduction of pain than BM ($P &lt; 0.005$), 8 weeks 2 and 4: ns</td>
<td>Univariate analysis (Fisher’s exact test)</td>
<td>2</td>
</tr>
<tr>
<td>Steroid preparation</td>
<td>Wright et al. [9]</td>
<td>38 joints as crossover (76)</td>
<td>HC acetate vs HC tertiary butyl acetate</td>
<td>Pain likert 0–4 (improved/not)</td>
<td>2, 4, 6, 8</td>
<td>2 weeks: only TBA statistically superior to placebo at 2 weeks ($P &lt; 0.02$), 4 weeks: both ns</td>
<td>Not stated</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: ACR, American College of Rheumatology; THA, triamcinolone hexacetonide; RA, rheumatoid arthritis; AS, ankylosing spondylitis; MPA, methylprednisolone acetate; HA, hyaluronic acid; BM, betamethasone; IA, intra-articular; HC, hydrocortisone; KL, Kellgren-Lawrence; VAS, visual analog scale; HAQ, health assessment questionnaire; HAD, hospital anxiety and depression scale; ns, non-significant; BMI, body-mass index; WCC, white-cell count; n/a, not applicable.
# Table 3 Factors Examined as Predictors to Intra-articular Steroid Injection in Hip Osteoarthritis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Author</th>
<th>Number Receiving Steroid</th>
<th>Method of Measurement</th>
<th>Outcome</th>
<th>Time Observed (Weeks)</th>
<th>Result</th>
<th>Statistical Method</th>
<th>Jadad Score</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical and structural joint factors</strong></td>
<td></td>
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<tr>
<td>US synovitis</td>
<td>Atchia et al. [27]</td>
<td>19</td>
<td>Capsule to neck distance &gt; 7 mm (no differentiation fluid vs synovium)</td>
<td>OARSI response</td>
<td>1, 4, 8</td>
<td>Synovitis predicts response at 4 weeks (P &lt; 0.05) OR 16.7 (1.4, 204)</td>
<td>Fishers Exact test</td>
<td>3</td>
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<tr>
<td>US synovitis</td>
<td>Robinson et al. [29]</td>
<td>120</td>
<td>US synovitis or capsular thickening examined separately</td>
<td>WOMAC response (15% improvement)</td>
<td>6, 12</td>
<td>Both ns</td>
<td>Spearman's r</td>
<td>n/a</td>
</tr>
<tr>
<td>US effusion</td>
<td>Qvistgaard et al. [28]</td>
<td>32</td>
<td>Not defined</td>
<td>Pain VAS; walking (absolute change)</td>
<td>2, 4, 12</td>
<td>ns at weeks 2, 4 (P = 0.26)</td>
<td>Linear approach to repeated measures, using model of PJ Diggle, based on maximum estimates of likelihood parameters.</td>
<td>4</td>
</tr>
<tr>
<td>Radiographic grade</td>
<td>Atchia et al. [27]</td>
<td>19</td>
<td>Croft grade (most 3–4)</td>
<td>Numerical rating scale for pain, OARSI response</td>
<td>1, 4, 8</td>
<td>ns</td>
<td>Univariate logistic regression</td>
<td>3</td>
</tr>
<tr>
<td>Radiographic grade</td>
<td>Qvistgaard et al. [28]</td>
<td>32</td>
<td>KL dichotomous (1–2 and 3–4)</td>
<td>Pain VAS; walking (absolute change)</td>
<td>2, 4, 12</td>
<td>ns (P = 0.13)</td>
<td>Linear approach using model of PJ Diggle, based on maximum estimates of likelihood parameters.</td>
<td>4</td>
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<tr>
<td>Radiographic grade</td>
<td>Lambert et al. [22]</td>
<td>31</td>
<td>KL</td>
<td>WOMAC response (15% improvement)</td>
<td>8</td>
<td>ns</td>
<td>Fishers Exact test</td>
<td>n/a</td>
</tr>
<tr>
<td>Radiographic grade</td>
<td>Robinson et al. [29]</td>
<td>120</td>
<td>KL dichotomous (0–2 and 3–4)</td>
<td>WOMAC response (15% improvement)</td>
<td>6, 12</td>
<td>Trend towards greater number responders at lower KL grades at week 12 (NS at numbers not quoted)</td>
<td>t-Test with Bonferroni correction</td>
<td>n/a</td>
</tr>
<tr>
<td>Variable</td>
<td>Author</td>
<td>Number Receiving Steroid</td>
<td>Method of Measurement</td>
<td>Outcome</td>
<td>Time Observed (Weeks)</td>
<td>Result</td>
<td>Statistical Method</td>
<td>Jadad Score</td>
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<tr>
<td>Radiographic grade</td>
<td>Deshmukh et al. [25]</td>
<td>217</td>
<td>KL categories (0–1, 2, 3–4)</td>
<td>Pain improvement VAS (50% improvement)</td>
<td>Immediate, 2</td>
<td>Higher response rate at 2 weeks in severe (KL 3–4) group than mild (KL0-1) OR 5.33 [CI 2.04-13.93], ( P = 0.001 )</td>
<td>Multivariable logistic regression</td>
<td>n/a</td>
</tr>
<tr>
<td>Radiographic grade</td>
<td>Plant et al. [23]</td>
<td>27</td>
<td>KL grade</td>
<td>Pain VAS (absolute change)</td>
<td>2</td>
<td>ns (( P = 0.6 ))</td>
<td>Mann–Whitney U</td>
<td>n/a</td>
</tr>
<tr>
<td>Radiographic grade</td>
<td>Plant et al. [23]</td>
<td>45</td>
<td>Pattern of radiographic change</td>
<td>Pain VAS (absolute change)</td>
<td>2</td>
<td>Less pain reduction in atrophic radiographic pattern (( P = 0.04 )) median change 0.9 cm cf. 7.5 cm in other groups</td>
<td>Mann–Whitney U</td>
<td>n/a</td>
</tr>
<tr>
<td>Radiographic grade</td>
<td>Flanagan et al. [24]</td>
<td>12</td>
<td>Charnley classification</td>
<td>Pain likert (absolute change)</td>
<td>1, 2, 3, 4</td>
<td>Poor response where concentric joint space narrowing (no measures of significance supplied)</td>
<td>Not stated (no measures of significance supplied)</td>
<td>4</td>
</tr>
<tr>
<td>Osteophyte grade on US</td>
<td>Robinson et al. [29]</td>
<td>120</td>
<td>Semiquantative grade</td>
<td>WOMAC response (15% improvement)</td>
<td>6, 12</td>
<td>ns</td>
<td>Spearman's ( \sigma )</td>
<td>n/a</td>
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<tr>
<td>Baseline pain</td>
<td>Atchia et al. [27]</td>
<td>19</td>
<td>Baseline numerical rating scale</td>
<td>NRS pain (absolute change)</td>
<td>1, 4, 8</td>
<td>ns</td>
<td>Univariate logistic regression</td>
<td>3</td>
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<tr>
<td>Baseline pain</td>
<td>Flanagan et al. [24]</td>
<td>12</td>
<td>Baseline pain likert</td>
<td>Pain likert (absolute change)</td>
<td>1, 2, 3, 4</td>
<td>Poorer response where higher baseline pain</td>
<td>Not stated (no measures of significance supplied)</td>
<td>n/a</td>
</tr>
<tr>
<td>Baseline pain</td>
<td>Robinson et al. [29]</td>
<td>120</td>
<td>Baseline WOMAC pain</td>
<td>WOMAC response (15% improvement)</td>
<td>6, 12</td>
<td>ns</td>
<td>Mann–Whitney U with Bonferroni correction</td>
<td>n/a</td>
</tr>
<tr>
<td>Baseline pain</td>
<td>Robinson et al. [29]</td>
<td>120</td>
<td>Baseline WOMAC stiffness</td>
<td>WOMAC response (15% improvement)</td>
<td>6, 12</td>
<td>Lower stiffness at baseline associated with responder status at 12 weeks ($P = 0.043$)</td>
<td>Mann–Whitney U with Bonferroni correction</td>
<td>n/a</td>
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<tr>
<td>Symptom duration</td>
<td>Flanagan et al. [24]</td>
<td>12</td>
<td>Duration of symptoms</td>
<td>Pain likert (absolute change)</td>
<td>1, 2, 3, 4</td>
<td>Poor response where symptom duration greater than 5 years</td>
<td>Not stated (no measures of significance supplied)</td>
<td>4</td>
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<tr>
<td>General patient characteristics</td>
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<tr>
<td>Age</td>
<td>Robinson et al. [29]</td>
<td>120</td>
<td>Standard</td>
<td>WOMAC response (15% improvement)</td>
<td>6, 12</td>
<td>ns</td>
<td>t-Test with Bonferroni correction</td>
<td>n/a</td>
</tr>
<tr>
<td>Gender</td>
<td>Robinson et al. [29]</td>
<td>120</td>
<td>Standard</td>
<td>WOMAC response (15% improvement)</td>
<td>6, 12</td>
<td>ns</td>
<td>t-Test with Bonferroni correction</td>
<td>n/a</td>
</tr>
<tr>
<td>BMI</td>
<td>Robinson et al. [29]</td>
<td>120</td>
<td>Standard</td>
<td>WOMAC response (15% improvement)</td>
<td>6, 12</td>
<td>6 weeks: higher BMI lower probability of response ($P = 0.026$) ns following Bonferroni correction. Week 12: ns</td>
<td>t-Test with Bonferroni correction</td>
<td>n/a</td>
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<tr>
<td>Characteristics of injection</td>
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<tr>
<td>Steroid dose</td>
<td>Robinson et al. [29]</td>
<td>120</td>
<td>80 mg vs 40 mg MPA</td>
<td>WOMAC response (15% improvement)</td>
<td>6, 12</td>
<td>Significant response only in 80 mg, not 40 mg, dose at 6 weeks ns</td>
<td>Mann–Whitney U with Bonferroni correction</td>
<td>n/a</td>
</tr>
<tr>
<td>Injection volume</td>
<td>Young et al. [26]</td>
<td>110</td>
<td>40 mg TA in 3 ml or 9 ml volumes</td>
<td>WOMAC (absolute change)</td>
<td>3</td>
<td>ns</td>
<td>ANOVA</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations: ACR, American College of Rheumatology; THA, triamcinolone hexacetonide; RA, Rheumatoid arthritis; AS, ankylosing spondylitis; MPA, methylprednisolone acetate; HA, hyaluronic acid; BM, betamethasone; IA, intra-articular; HC, hydrocortisone; KL, Kellgren–Lawrence; VAS, visual analog scale; HAQ, health assessment questionnaire; HAD, hospital anxiety and depression scale; ns, non-significant; BMI, body-mass index; n/a, not applicable.
and 3 ultrasound (US) guidance [27–29]. Four studies contained a placebo arm [22,24,27,28], 2 of which also compared steroid with hyaluronic acid injection [27,28].

### Clinical and Structural Joint Factors

Three studies examined US-assessed features of inflammation with relation to clinical response. A placebo-controlled trial including 19 patients receiving high dose IA corticosteroid (120 mg methylprednisolone) defined “synovitis” as those with capsule to femoral neck measurement >7 mm [27]. Subjects with synovitis were significantly more likely to be termed responders according to OsteoArthritis Research Society International (OARSI) criteria at 4 weeks (OR 16, CI 1.4–204) than those without synovitis. However, no significant differences between these groups was reported with respect to the primary outcome measure of a numerical rating scale for worst pain or other secondary measures including WOMAC pain subscale.

Two larger studies using lower steroid doses (40–80 mg methylprednisolone) did not detect any association between US appearances and outcome [28,29]. One of these, an open-label study of 120 patients, examined effusion (defined as hypo- or anechoic fluid along the femoral neck, deep to the capsule) and semi-quantitative capsular thickness but found neither to be associated with WOMAC response at 6 or 12 weeks [29]. The second study [28], a placebo-controlled trial including 32 patients receiving steroid, found no association between US effusion (not defined) and response at time-points between 2 and 12 weeks.

All 7 studies examined radiographic grade in relation to response. Two [22,28] examined KL grades as dichotomous categories (grade 1–2 vs grades 3–4) and 1 [25] as 3 categories (grade 0–1, grade 2, and grade 3–4), 2 [22,23] analyzed individual KL grades, 1 used Croft grading [27], and 1 [24] used Charnley classification [30]. Four of the studies using KL grading detected no significant association between radiographic grade and response, although 1 reported a trend between lower radiographic grade and better response at week 12 (statistics not supplied) [29]. One retrospective study [25] of 217 patients assessed response by patient-VAS for percentage pain improvement immediately following and at approximately 2 weeks after fluoroscopically-guided injection of 80 mg methylprednisolone by a single experienced operator. Adjusting for age and gender, the authors reported a higher rate of response at 2 weeks in patients with severe (KL 3–4, OR 5.33 [CI 2.04–13.93], P < 0.001) radiographic changes, compared with those with mild (KL 0–1) changes. The study using the Charnley classification [24] reported less pain relief in patients with concentric pattern of joint space narrowing but did not provide statistical data supporting this. Finally, one of the studies using KL classification [23] also examined the effect of subtypes of radiographic change, characterized by bone response [31]. Pain relief at 2 weeks was significantly lower in patients showing an atrophic pattern of disease compared with other patterns (P = 0.04). No others studies using this or the Charnley classification were identified.

A single study [29] examined semi-quantitative US osteophyte grade and did not detect any association with response.

Three studies examined the effect of baseline pain scores [24,27,29]; 2 found no effect of baseline pain on clinical response, while 1 [24] reported lower pain relief in patients with higher baseline pain and in patients with symptom duration of over 5 years, but did not supply statistical data or measures of significance to support this. One study [29] found lower baseline stiffness (measured by WOMAC) associated with response (defined by 15% reduction in WOMAC score) at 12 weeks (P = 0.043). No other studies reported baseline stiffness as a predictor of response.

### General Patient Characteristics

The same study that examined stiffness [29] also examined demographic factors including age, gender, and BMI. While age and gender had no relationship with response, patients with higher BMI were initially found to have a lower probability of being responders at 6 weeks (P = 0.026), although this did not remain significant after Bonferroni correction.

### Psychological Factors

None of the 8 studies in hip OA reported on psychological variables.

### Factors Relating to the Injection

One open-label study compared 40 mg and 80 mg doses of methylprednisolone, using the WOMAC index [29]. Forty milligram produced statistically significant reduction in pain at 6 but not at 12 weeks, whereas 80 mg produced significant reductions at both time-points. Defining clinically significant response as 15% reduction in WOMAC, only the 80 mg group showed significant response at 6 weeks, indicating a possible dose effect.

A prospective RCT of injection of 110 patients compared injection of Triamcinolone acetonide in different injection volumes of 3 ml or 9 ml and found no significant differences between the groups at 3 months [26].

### DISCUSSION

This systematic review found very limited evidence for predictive factors of pain relief following IA corticosteroid injections in OA of knee and hip. Considering the longstanding and widespread use of IA corticosteroid injections in hip and knee OA, the lack of relevant research and knowledge on predictive factors is quite surprising.
In general, where predictive factors have been identified, findings are based on single studies, with at least one other study failing to reproduce the observation.

The relevance of effusion as a predictor of response is of particular interest. The finding that effusion and the aspiration of synovial fluid at the baseline in one study predicted greater reduction of pain at 1 week [10] and influenced recommendations on the use of IACI in clinical guidelines for knee osteoarthritis [32]. However, this finding has not been replicated in other studies measuring comparable time-points [11,13,14]. In the KIVIS study [11], baseline knee effusion was found to be associated with a significantly greater reduction WOMAC pain subscale at 26 weeks following injection, whereas in patients without baseline knee effusion, WOMAC pain score deteriorated from baseline. No difference between these groups was reported at earlier time-points in this study. It is attractive to suggest that baseline effusion may predict duration of response to IACI. However, the relevance of this intriguing finding remains unclear since placebo-controlled studies have not provided unequivocal evidence of efficacy of steroid over placebo at 26 weeks. An alternative explanation for the finding could be that patients with effusion at baseline represented a group in whom a short term increase in pain had occurred accompanying a recent inflammatory flare and that the difference at 26 weeks was created by natural regression to the mean rather than a specific effect of steroids. This problem illustrates one of the difficulties in interpretation associated with our decision to include studies not containing a placebo arm in our review. The advantage of including these studies was that that they frequently contained larger numbers of patients in their analyses to allow for analysis of predictive factors.

A further area of interest is radiographic change as a predictor in hip OA injections, but despite some concordance in findings, the overall level of evidence remains inconclusive. The largest study of 217 patients [25], while conducting multiple regression analysis, was retrospective and assessed responses using “improvement of pain VAS” after the procedure rather than assessing pain VAS at baseline and follow-up. Furthermore, 40% of patients in the mild OA group had normal X-rays and it could be argued that these had another source for their pain other than hip OA, which would also explain the lower immediate pain relief rate reported in that group. Although the smaller prospective study by Plant et al. [23] identified an atrophic radiographic pattern associated with less frequent response to IA steroids, it found no association between KL grade and response. The strength of the study using Charnley classification [30] is limited by the small sample of only 12 patients receiving steroid and the lack of description of statistical analysis. In the case of knee OA, the KIVIS study demonstrated significantly greater pain reduction at 26 weeks in those patients with milder radiographic grade than those with more severe radiographic disease.

With the exception of anxiety and depression, which in a single study where not found to be predictive of response, these and other psychological factors have been ignored as potential predictors.

The main limitation of available evidence is that very few studies were designed to determine predictors of response. Analyses for predictors of response were generally conducted post hoc, once the main comparisons for efficacy of IA corticosteroid injections had been performed. As a result, practically all studies would appear to have insufficient power to adequately address potential associations. This may explain the high number of incidences in which no associations with clinically plausible predictors were detected and this presents a potential source of bias.

Further difficulty is created by the great variation in trial design in terms of intervention drugs and doses, time-points for outcome assessment and methods of assessment of patient characteristics. For instance, 4 different scoring systems for radiographic grade are used across the 5 studies addressing radiographic grade in knee OA [10,18,20]. Of particular importance are variations in outcome measures. Some studies report statistically significant differences in the change of pain between groups [10,18], but such changes may or may not be clinically significant. Other studies define “responder status”, usually according to changes considered clinically significant [13,29]. This approach has obvious advantages but may increase the probability of subtle effects being missed in smaller samples. Even statistical analyses vary considerably between studies, but it is notable that most of the positive associations reported (including those of greater pain reduction in patients with knee effusion and hip synovitis) are products of univariate analyses [10,27], whereas studies which produce negative results are often those using logistic regression and/or correct for potential confounders [11,13,17,28,29]. In addition, while the studies do present data, in general these describe whole group effects rather than those of the subgroups in which we are interested. The exception to this rule is in studies which illustrate specific positive findings with relation to predictors of response. The combination of such data, were it possible to do so, might introduce bias in favor of positive associations.

This systematic review may have several limitations. Firstly, we have limited our investigation to English language publications. We have alluded to the difficulties in drawing conclusions from studies without placebo-controlled arms. Although we provide Jadad scores for the RCTs included, these may not provide an accurate impression of the quality of secondary analysis, as exemplified by a study which attracted a Jadad score of 4 but did not supply details of statistical analysis or measures of significance in support of observations made in describing a group of 12 treated patients [24]. Instead, we have considered specific characteristics
such as study size and type of statistical analysis, to give an impression of quality and relevance of individual studies. We limited the scope of our review to outcomes based on pain, because it is the outcome for which efficacy of IA corticosteroid injections over placebo has been demonstrated. We have, however, reported results relating to composite outcome measures such as the OARSI response from studies meeting our inclusion criteria. Finally, we suspect that there may be relevant studies that have not been published due to negative results.

We did not find other reviews addressing response predictors to IA corticosteroid injections as the primary question, but several reviews relating to the efficacy of IA injections in knee osteoarthritis considered the subject. The 2006 Cochrane review [5] recognized the controversy surrounding the possible association between effusion and response, as do others [6,33]. It also offers guarded agreement regarding the evidence in favor of triamcinolone hexacetonide over methylprednisolone in the short term, as does a review by Hepper et al. [34]. Our results suggest that a dose effect may exist in hip OA. Arrol and Goodyear-Smith [6] asserts that a similar effect may exist in knee OA, while the Cochrane review found insufficient evidence to support such a conclusion.

Other Potential Predictive Factors

This review has identified a number of predictive factors examined, but also illustrated the paucity of solid data. A number of plausible predictive factors have so far not been tested.

The observation in a trial of greater pain reduction in patients with effusions [8] has provoked a debate which has focused almost exclusively on the possible role of inflammation in knee OA and its effects on the response to IA corticosteroid injections [35]. This is, perhaps, logical since steroids are used primarily as treatments for inflammation and there is now ample evidence that synovial inflammation in knee OA is both common [16,36] and may correspond with symptoms [37] and disease progression [38]. However, the alternative hypothesis provided to explain the effect of effusion; that injections might be more effective in patients with effusion because of a higher probability of entering the joint cavity accurately, has received surprisingly little attention and has not been systematically investigated. While few would now advocate hip injections without recourse to imaging guidance, it is commonly perceived to be unusual for injections to fail to enter the knee joint in routine procedures based on clinical landmarks. However, some studies have demonstrated figures as high as 30% [39], which our own, unpublished, observations reflect. One study [21] did examine the possible importance of intra-articular placement on response in comparing injections (assumed to be) given by the intra-articular route with identical injections administered to the 4 quadrants of the margin of the patella from the mid point of the medial border and the midpoint of the lateral border and found no difference in response. However, the authors acknowledge that the study lacked power to allow firm conclusions relating to effectiveness. It is known that US guidance can improve the accuracy of injection but studies employing it have rarely controlled for the potential placebo effect of the technique itself. An exception is the study by Cunnington et al. [40], involving injection of a large variety of inflamed joints in different forms of inflammatory arthritis: this did not demonstrate any difference in pain reduction between injections that entered the joint and those that failed to do so. Despite this, it seems surprising that no investigation has been made of whether improving accuracy could improve outcomes of injections in knee OA.

A second area that this review identified as practically unexplored is the effect of psychological factors on responses to IA corticosteroid injections. We found only 1 article addressing any psychological variable as a potential predictor [13]. There are several reasons why psychological factors are likely to influence the reported response to IA corticosteroid injections. Firstly, and critically, all outcomes relating to pain (and most relating to function) are patient-reported and therefore subject to patient perceptions and expectations. For instance, depression has been shown to influence WOMAC scores [41]. Secondly, psychological factors have been demonstrated to explain considerable variance in pain in knee OA [42] and to explain differences in reported disability [43–45]. With respect to the outcome of pain-relieving procedures, there is evidence that adverse psychological factors predict persistent pain following technically successful total knee replacement [46–49].

While US imaging has been used to examine the potential role of synovitis as a predictor of response to IA corticosteroid injections, no studies have used MRI imaging. MRI has important advantages over US in studying OA, including the ability to image structures inaccessible to US and to detect bone marrow lesions, which have been shown to be associated with pain in knee OA [50].

Suggestions for Further Research

Previous research has not provided evidence of reliable predictors of response to IA corticosteroid injections in knee and hip OA. Given the scale of the problem of OA, numbers of IA corticosteroid injections given in clinical practice and the lack of other effective non-surgical treatments for pain, further studies to determine predictors are required. On the basis of our review of the literature, we would suggest that such studies should be: (1) designed and powered to detect predictors of response as a primary objective; (2) use well recognized standardised and clinically relevant outcome measures; and (3) examine factors with a strong theoretical or empirical basis, whether they are “physical” or “psychological”.

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CONCLUSIONS

Previous research has not identified reliable predictors of response to IA corticosteroid injections, a widely practised intervention in knee and hip OA. Further studies are required if this question is to be answered.

KEY MESSAGES

- Evidence for predictors of pain relief after IA steroid injection in knee and hip osteoarthritis is weak.
- This includes features of inflammation and radiographic severity.

REFERENCES

APPENDIX A

Valianded Instruments and Grading Systems

For a list of validated instruments and grading systems see Tables A1–A4.

### Table A1 Outcome Measures

<table>
<thead>
<tr>
<th>Instrument/Classification</th>
<th>Citation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Ontario and McMaster Universities OsteoArthritis Index (WOMAC)</td>
<td>Bellamy J Rheum 1988; 15(12):1833–40</td>
<td>Questionnaire assessing OA symptoms, comprising 24 questions across 3 domains (pain, function, and stiffness), answered by 100 mm VAS or Likert response. Higher scores denote more severe symptoms or limitations.</td>
</tr>
<tr>
<td>Osteoarthritis Research Society International (OARSI) responder criteria for OA research trials</td>
<td>Pham TJ Rheum 2003; 13(7):1648–54</td>
<td>Response criteria recommended by OARSI for use in OA clinical trials following consensus exercise. Includes measurement of pain, functional limitation and patient global assessment by 100 mm VAS. Response is defined EITHER by improvement of 50% (and absolute change of 20 mm) in a single domain, OR 20% improvement and 10 mm absolute change in 2 or more domains.</td>
</tr>
</tbody>
</table>

### Table A2 Psychological Questionnaires

<table>
<thead>
<tr>
<th>Instrument/classification</th>
<th>Citation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Anxiety and Depression Scale</td>
<td>Zigmond AS. Acta Psychiatr Scand 1983; 67(6): 361–70</td>
<td>Questionnaire assessing symptoms of depression and anxiety. 14 questions; divided into domains for depression (7 questions, scores range 0–21) and anxiety (7 questions, range 0–21). Higher scores denote higher levels of depression and/or anxiety.</td>
</tr>
<tr>
<td>Instrument/Classification</td>
<td>Citation</td>
<td>Grade</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------</td>
<td>-------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Possible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 (Mild)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Marked narrowing of joint space narrowing, definite osteophytes, sclerosis and cyst formation, deformity of femoral head and acetabulum</td>
<td>Croft grading for radiographic hip OA (modification of KL grading)</td>
<td>4 (Severe)</td>
</tr>
<tr>
<td>Croft grading for hip OA; minimal joint space (measured from femoral head to acetabulum)</td>
<td>Croft P. Am J Epidemiol 1990;132:514–22</td>
<td>Grade</td>
</tr>
<tr>
<td>Wroebleski B. JBJS 1982; 64B(5): 568-9</td>
<td>Classification based on radiographic morphology, dividing hip OA into 11 categories of: upper pole joint space narrowing and femoral head flattening (grade 1–3), medial pole disease, protrusio acetabuli, concentric joint space narrowing, destructive change (head type, acetabular type, tuberculosis type), quadranctic head necrosis, congenital subluxation/dislocation. Categories may co-exist.</td>
<td></td>
</tr>
<tr>
<td>Solomon. JBJS 1976; 58B(2): 176–83</td>
<td>Classification of 6 categories of hip OA, based on background pathology and radiographic change: Major previous pathology (including trauma and inflammatory arthritis), acetabular dysplasia, femoral head tilt, “post inflammatory degenerative” (atrophic–none had known history of inflammation), steroid arthropathy, alcoholic arthropathy.</td>
<td></td>
</tr>
</tbody>
</table>

*Insufficient evidence of instrument validation.
*Categories associated with poor response in included studies. Share characteristics of widespread joint space narrowing and sparse osteophytes.
<table>
<thead>
<tr>
<th>Instrument/Classification</th>
<th>Citation</th>
<th>Definitions of US-assessed synovitis and effusion applied in EULAR US survey of knee OA</th>
</tr>
</thead>
</table>
|                          | D’Agostino M. Ann Rheum Dis 2005;64:1703–1709 | Synovitis: “hypechoic synovial hypertrophy with thickness > 4 mm and diffuse or nodular appearance, with the knee semiflexed at 45° on the median longitudinal plane crossing the quadriceps tendon.” The morphology of inflammatory synovitis was evaluated on a 3 point categorical scale as absent, nodular, or diffuse.  
Effusion: “anechoic area in the suprapatellar recess, with the leg in full extension, maximum depth measured with a longitudinal scan.” Absent if effusion depth < 4 mm and present if > 4 mm |
Chapter 4.0 Methods

4.1 Study Design and Overview

The research work described in this thesis took the form of an observational cohort study with an integral pilot phase of patients with symptomatic knee osteoarthritis treated with an intra-articular steroid injection. Baseline assessment of physical symptoms, measures of psychological health and other potential predictor variables (including physical signs and imaging parameters) were performed, with subsequent outcome assessments at three and nine weeks.

4.2 Setting

Fieldwork was conducted within the Dudley Group NHS Foundation Trust and was based at Russells Hall Hospital in Dudley. This is a busy district general NHS Teaching Hospital serving a predominantly urban population of around 400,000 people.

4.3 Recruitment

Following review, the pilot phase and study were granted ethical permissions by the South Birmingham and Yorkshire and Humber Research Ethics Committees respectively (references 11_WM_0102 and 12_YH_0457).

Study participants were recruited amongst patients attending routine rheumatology and orthopaedic outpatient clinics within the Dudley Group NHS Foundation Trust. Those considered eligible for inclusion were patients with knee symptoms caused by osteoarthritis and recommended by their treating physician to have an intra-articular steroid injection as part of their clinical management. Potentially eligible participants were identified by hospital clinicians who, provided the patient consented to be approached by the research team, forwarded their details to the research team (GH) and also gave them a patient information sheet. Subjects were subsequently contacted by the research team who arranged a review for consent, baseline assessment and the injection.
4.4 Inclusion and Exclusion Criteria

4.4.1 Inclusion criteria
Men and women aged 40 years or over were eligible for inclusion if i) they satisfied the ACR criteria for knee OA based on clinical and/or radiographic criteria (21), or ii) if they had evidence of OA in the context of rheumatoid arthritis (RA). This was defined as; i) radiographic joint damage on knee radiograph AND, ii) pain characteristic of degenerative disease of greater than 6 weeks duration AND, iii) knee symptoms attributed by their clinician to degenerative rather than inflammatory disease AND, iv) their RA was judged by the referring clinician and investigator to be well controlled. Additional criteria were that the IACI had been recommended by their treating physician as part of their routine care and that their knee pain was greater than 20mm on the standardised (0-100 mm) WOMAC (Western Ontario and McMaster Universities) pain subscale (233).

4.4.2 Exclusion Criteria
Exclusion criteria included inability to provide informed consent, contraindication to steroid injection (including hypersensitivity to any of the components of injection), active infection, bleeding diathesis, inflammatory arthritis other than rheumatoid arthritis, oral prednisolone dose greater than 7.5mg daily, intra-articular or intramuscular steroid injection within the preceding 3 months and/or a diagnosis of fibromyalgia.

4.5 Visit Schedule
Participants attended for consent and baseline assessment followed by arthrocentesis and an intra-articular steroid injection. They attended three weeks later for further assessment and returned a final outcome questionnaire by post after nine weeks.
Participants failing to return the final outcome questionnaire within 10 days of the due date received a telephone reminder.

The first time point for outcome assessment was at three weeks. This was chosen for two reasons. Firstly, it represents a point at which the intervention was more effective than placebo according to systematic reviews (146-148). Secondly, a previous open-label clinical trial of corticosteroid injection using the WOMAC instrument (153) suggested that at this point a significant proportion to patients (50%) would be responders to treatment, as defined as a 40% reduction in WOMAC pain subscale from baseline.

The second time point for outcome assessment was at nine weeks. Systematic reviews (147;148) do not provide unequivocal evidence of specific effect of IACI at 9 weeks but this relates to paucity of data rather than negative studies. Arrol (146) reported that pooled analysis of data from two high quality placebo controlled studies suggested that IACI are effective at 12 weeks.

4.6 Outcome measures and calculation of responder status.

4.6.1 WOMAC index

Physical symptoms of osteoarthritis were assessed using the WOMAC (Western Ontario and McMaster Universities Osteoarthritis) index, version 3 (233). The WOMAC index is an internationally recognized and widely used multi-dimensional patient reported questionnaire that measures symptoms over the preceding 48 hours. It was designed for and has been validated for osteoarthritis and has been used in numerous osteoarthritis clinical trials. It consists of 24 questions, grouped across three domains of pain, stiffness and function, with higher scores representing more severe symptoms. It may be answered either using visual analogue scales or Likert scales. The Visual Analogue Scales were chosen to facilitate calculation of percentage change that could be registered after treatment. The WOMAC has been shown to have good measures of internal consistency (234) and test re-test reliability (235) and to be responsive to change (234).
4.6.2 WOMAC response

The definition of response to therapy (based on WOMAC) employed was a minimum 40% reduction in WOMAC pain subscale from baseline to follow-up (referred to hereafter as ‘WOMAC response’). This was chosen since it is suggested to represent the minimum clinically significant and meaningful improvement in pain following an intervention (236).

4.7 Assessments

4.7.1 Demographic information and past medial history.

Relevant information relating to participants’ medical history was obtained using a standard interviewer-administered pro-forma. Information recorded included age, gender, duration of rheumatoid arthritis if present, duration suffering frequent knee pain, presence or absence of significant pain in other body area during last week (completing 100mm VAS for overall severity of pain in worst site other than knee, if present), past medical history, current medication, whether previous IA steroid injection given and recall of effectiveness of last injection (100mm VAS). The pro-forma contained a checklist to allow recording of eligibility criteria according to ACR for patients with primary OA (21).

4.7.2 Psychological scales

Participants were asked to complete the following psychological questionnaire instruments:

4.7.2.1 Revised Illness Perception Questionnaire

Illness perceptions were measured with the revised version of the Illness Perception Questionnaire (IPQ) (212). The IPQR is a patient-administered questionnaire examining patients’ beliefs about their illness. It contains 38 items relating to illness perceptions and 18 items relating to possible causes of their illness. Individual items are
represented as statements that invite responses on a 5 point Likert scale (strongly disagree to strongly agree). The domains of principal interest in this study were Treatment Control, Personal Control and Consequences, based on both theoretical considerations and on the basis of scores observed at the interim analysis. The ranges of possible scores for the subscales are 5-25 for Treatment Control, 6-30 for Personal Control and 6-30 for consequences. Higher control scores represent a stronger belief that the course of one’s illness may be influenced by treatments or by personal attitudes/ behaviour respectively and in the case of consequences that the illness has a significant impact on the individual’s life overall. The IPQR has been shown to have good internal consistency (212) (Cronbach’s α for personal control and treatment control domains of 0.81 and 0.80 respectively). Test-retest reliability in general has been shown to be acceptable at three weeks (correlation 0.46-0.88), although weakest for personal control (0.46).

A previous meta-analysis of studies of the effect of illness perceptions performed in 2003 (237) suggested that the IPQ (and, in the more recent studies the IPQR) was the instrument chosen for measuring Illness perceptions in around 75% of studies. Alternative methods have only been used in individual studies and are often dependent on interview methods and individual factor analysis. By contrast, the IPQR has been validated and used in several studies of OA, with favourable reports of its performance characteristics (238). This instrument therefore provided an obvious choice for use in this study, with the additional advantage over the IPQ of allowing determination of treatment control and personal control separately.

4.7.2.2 Pain Catastrophizing Scale.

Pain catastrophizing was measured using the Pain Catastrophizing Scale (PCS) (239). This is a self administered patient questionnaire that assesses patients’ tendency towards pain catastrophizing. It is the most widely used tool for examining pain catastrophizing, the only tool designed exclusively for this indication and has essentially replaced the subscale of the Coping Strategies Questionnaire (240). The PCS contains 13 items, expressed as statements describing a particular thought or feeling
related to pain, to which patients respond on a 5 point scale. These items are grouped across the three domains of rumination, magnification and helplessness. The domains may be examined individually or scores may be summated to produce a total score (range 0-52). Higher scores represent a greater tendency to catastrophizing. The pain catastrophizing scale has been shown to have good overall internal consistency (239) (Cronbach’s α for 0.87, 0.60 and 0.79 for rumination, magnification and helplessness respectively).

4.7.2.3 AIMS 2 depression subscale

Depression was measured at three and nine weeks using the depression scale of the AIMS 2 questionnaire (241). This consists of 5 questions, answered using a 5-point Likert response. The possible range is 5-25, with higher scores indicating greater symptoms of depression respectively. The AIMS2 was selected as one of two questionnaires (AIMS and HADS) considered to have been designed to make them appropriate for use in patients with arthritis. The performance of the two scales has not been compared directly in OA. The AIMS2, although originally designed for use in rheumatoid arthritis, has been validated and shown to have good properties in OA (242). The second instrument, the Hospital Anxiety and Depression Scale (HADS), intended for use in hospital outpatients, attempted to exclude biological symptoms of depression which could be caused by organic illnesses. It has been employed in previous studies of arthritis, including one study of IACI (157) However, it does contain items which could relate to musculoskeletal disease (most notably “I feel slowed down all the time”) which may result in lack of discrimination for its use in measuring depression in patients with joint disease and it was therefore felt to be less appropriate for use than the AIMS2.

4.7.3 Physical and disease related characteristics

Height and weight were assessed in a standard fashion to calculate body mass index (as mass in Kg divided by squared height in metres). Symptoms of osteoarthritis
including pain, stiffness and function were assessed using the WOMAC index, as described above. An examination of the index joint was performed and presence of clinical effusion, local heat and local tenderness were documented and a tender and swollen joint count and patient global VAS for arthritis was recorded for patients with rheumatoid arthritis (RA). DAS 28 (Disease Activity Score, based on 28 joints) (243) is a widely used composite score of current RA activity applied in clinical rheumatology and research practice. It is calculated using the number of swollen and tender joints detected on clinical examination (including any of PIPJ, MCPJ, wrist, elbow, shoulder and knee joints), patient reported VAS for global arthritis activity and a serological marker representing inflammation (either CRP or ESR). A venous blood sample was also therefore acquired from all patients in the study in order to measure CRP in RA patients but also measurement of high sensitivity CRP (hsCRP) as a measure of comparing systemic inflammation between primary and secondary OA groups. However, it is recognized that DAS 28 has limitations in patient groups outside those with early arthritis, particularly those with secondary OA in whom symptoms due to damage lead to elevated subjective scores.

4.7.4 Imaging

4.7.4.1 Radiographs

Following consent, participants had plain radiographs of the affected knee in 3 planes (anterior-posterior, lateral and skyline views). These were acquired using standard hospital protocols by a team of radiographers trained in acquisition of standardised radiographs for research studies. For patients with adequate x-rays in 3 planes within the previous 6 months, repeat images were not undertaken.

Radiographs were evaluated by two observers (GH and RK, co-supervisor) blinded to patient clinical information according to the system based on individual radiographic features (244), using a standard atlas (245). Separate grades were allocated to individual features of osteophyte and joint space narrowing for the tibiofemoral and patellofemoral compartment. Each feature was scored between 0 and 3, with 3 being the most severe and where osteophyte grade 1 is said to be equivalent to Kellgren
Lawrence grade 2 (ie definite osteophyte) (245). Examination of individual features offers more discrimination than systems such as that by Kellgren-Lawrence (43). Scores were compared and consensus reached after discussion in case of disagreements. This grading system has been validated for osteoarthritis, including assessment of the patellofemoral joint. The highest radiographic grade for each feature at any of the 3 knee joint compartments (medial-tibiofemoral, lateral tibiofemoral and patellofemoral) was used for analysis.

4.7.4.2 Ultrasound Assessment

Ultrasound assessment was performed at baseline by the PhD student using a Siemens Antares, 7-13.5 MHz transducer (Siemens, Erlangen). Ultrasound protocols for image acquisition were the same as those used in an observational study of patients with arthritis, prior to knee injection (246). Measurements were conducted in each of medial, mid and lateral regions of the suprapatellar pouch (SPP), as defined by the patellar borders. Joints were examined in relaxed maximum extension for grey-scale evidence of effusion or synovial hypertrophy. Grey-scale is a term used in ultrasound practice to describe appearances seen on a plain 2D, B-mode ultrasound image without the use of specialized techniques such as power Doppler imaging. The definition of effusion was that of the OMERACT consortium (Wakefield et al. 2485-87), namely the presence of “anechoic, dispersible material” within the supra-patellar pouch. In describing US images, the densities of tissues visualized are described relative to the known appearance of subcutaneous fat. Material of the same density as subcutaneous fat is referred to as ‘isoechoic’. ‘Anechoic’ refers to material on ultrasound which appears black, returning little or no signal to the transducer. ‘Dispersible’ refers to the property of material to be completely displaced by transducer pressure, implying a liquid consistency. In keeping with definitions laid out in a large multi-centre EULAR cohort study of knee OA (40), a measurement of 4mm fluid at a single site in the SPP was viewed as abnormal and considered to represent effusion, although measurements were recorded as continuous data. Similarly, the definition of synovial hypertrophy applied was that used by the EULAR survey of knee OA, namely a hypoechoic or less commonly hyperechoic layer within the SPP which is
not dispersible and measures at least 4mm in depth. The presence of synovial hypertrophy and predominant pattern of synovial hypertrophy present (i.e. homogenous or polypoid) was recorded also for each site.

In the presence of any area of synovial hypertrophy, power Doppler imaging was employed in this area. Power Doppler sensitivity was adjusted to the maximum possible without the creation of artefact. Efforts were made to eliminate probe movements in order to prevent movement artefact. In order to maximize sensitivity, ‘gel stand-off’ was employed where possible, in which the operator attempts to ensure that the probe exerts no pressure on the tissues that could compress vessels and thus obscure Doppler signal by maintaining a layer of gel between probe and tissues. Power Doppler signal was graded in a semi-quantitative fashion frequently used for studies of this kind between grade 0 (absent), 1 (mild, single visible vessel), grade 2 (moderate, two or more areas of visible vessel) and grade 3 (severe, 50% or more of synovial tissue occupied by vessel) (247).

4.8 Intervention

Following the baseline assessments subjects had arthrocentesis and injection of steroid to the painful knee. This is described in more detail below.

4.8.1 Aspiration and injection of index joint

Injection of the index joint was performed according to usual clinical practice by clinicians (four consultant rheumatologists and three specialist registrars in rheumatology) aware of the study protocol and proficient in knee injection techniques. Following verbal consent for knee injection, the clinician examined the knee, determining whether clinical effusion was present and decided on the anatomical approach they would use to inject the knee. The skin was prepared with chlorhexidine solution and anaesthetized at the point of injection using ethyl chloride spray (Cryogesic, Ennogen). Under aseptic technique, a 21 gauge needle was inserted and
advanced into the joint. When the clinician was satisfied with placement of the needle, a syringe was used to attempt to aspirate any synovial fluid present. Following aspiration, a syringe containing 40mg triamcinolone acetonide (Kenalog, Bristol-Meyers Sqibb), 4ml 1% lignocaine and 2ml atmospheric air was connected to the needle and injected. At the time of injection, an ultrasound probe was applied to the midline SPP in order to capture an air-arthrosonogram (described below). The purpose of this was to determine whether or not the needle was within the joint. Following the procedure, the patient was asked to rest the joint for 24 hours, in keeping with usual clinical practice within the department.

4.8.2 Assessment of accuracy of injection

4.8.2.1 Ultrasound air arthrosonogram procedure

Accuracy of the injection was assessed by the presence of an air arthrosonogram on ultrasound scanning(218). For the purposes of this study an air arthrosonogram was defined as positive where free, mobile air could be seen within the joint cavity, including the supra-patellar pouch on an ultrasound image acquired either during or after joint injection. Air bubbles have three characteristic ultrasound properties that make them easy to identify in dynamic scanning. Firstly they are intensely hyperechoic, secondly they create ‘posterior acoustic shadowing’; that is a black area deep to the air in which nothing can be seen since no sound waves are able to penetrate beyond the air. Lastly, they are mobile in fluid and float to the surface.

In the absence of detectable effusion, the group who first described the use of the air arthrosonogram technique acknowledged that mobile air was sometimes difficult to detect, since there was no significant or dispersible fluid mass in which to demonstrate the air post-injection(229). It was, however, possible in these cases to witness briefly the movement of air into the midline SPP at the time of injection.

In order to maximize the probability of being able to visualize a positive air arthrogram, a probe with a sterile probe cover was placed in the midline suprapatellar pouch (SPP) in a longitudinal orientation at the time of injection and a video clip recorded. Next, a
systematic scan of the SPP was then performed immediately after the injection and video documentation made of air bubbles within synovial fluid, if present, with probe pressure used to demonstrate mobility. If no air bubbles were detected, a standard video clip of the SPP at the portal of injection was recorded in addition to the midline view at the time of injection, to document a visual record of the negative result. Where air bubbles are visualized within subcutaneous tissue outside the SPP (therefore having the contrast characteristics of air but not mobile) a video clip demonstrating this was also recorded as additional evidence of extra-articular injection.

Participants were classified as having positive or negative air arthrosonogram though neither the subject nor the treating clinician was informed of the US findings. Images of air arthrosonogram assessments were recorded onto compact discs.

4.8.2.2 Reliability testing of air arthrosonogram technique

The air arthrosonogram technique is well described both in ultrasound practice (229;248) and using plain radiographs (249). Some measures of its inter-observer reliability have been made previously (248).

Inter-observer reliability of the technique in this study was calculated by presenting a proportion of clips recorded during the study to three observers. The process was developed by the student. Twenty clips classified as representing positive and twenty negative air arthrosonograms were selected at random from the final study sample. One of these observers (GH) was the sonographer for the study and initially classified the arthrograms at the time of acquisition. One of these observers was Dr Rainer Klocke and the second was Dr Aabha Sinha, consultant radiologist at Russells Hall Hospital. Both are experienced in musculoskeletal ultrasound but neither performed ultrasound assessments in this study. All observers were blinded to clinical and outcome data. The two additional observers received verbal training in the operational definition of a positive and negative air arthrosonogram, reinforced and illustrated by two further video clips from the study representing positive and negative controls. Video clips were viewed in random order on a high quality viewing screen designed for
radiologist’s assessment. All three observers viewed recorded clips simultaneously and recorded their impression of whether a positive arthrosonogram was present according to the criteria given and recorded this impression as either positive or negative. Classification was made independently without conferring. If one of the observers was unable to decide how to classify a clip after one viewing then the clip was repeated until all three observers were satisfied as to how to classify it.

Kappa statistics were then calculated to determine inter-observer variability for each pair of raters and a mean kappa for the three rater pairs calculated.

4.9 Visit Schedule

This section describes the visit schedule, and the key assessments undertaken at different time points. These are summarized also in Table 2.

Table 2: Scheduled assessments taking place in study.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Baseline</th>
<th>Week 3</th>
<th>Week 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Written Consent</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion and exclusion criteria</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history and demographic information</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS for previous injection (if applicable)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Examination</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measure height and weight</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOMAC pain subscale</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>IPQR</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIMS 2 depression subscale</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PCS</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee X-ray</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous blood sample</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspiration and Injection</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment of arthrosonogram</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.9.1 Baseline

The first appointment included consent, assessment of inclusion and exclusion criteria and also baseline investigations. Participants had received the patient information sheet at least 24 hours before their appointment and had the opportunity to ask any questions about the study before signing a standard consent form at the beginning of the appointment and prior to any study procedures being performed.

Participants who declined to take part in the study received their planned injection as part of their clinical care following standard verbal consent, as per usual clinical practice.

Consenting participants were screened for inclusion and exclusion criteria according to section 4.4.1 and 4.4.2. This included age, assessment of ACR criteria and WOMAC pain subscale score as well as specific exclusion criteria as described.

Participants who had not had x-rays of the affected knee within the last 6 months were required to have x-rays in three planes as described above. This was undertaken prior to their IACI.

Consenting participants found to be ineligible to participate in the study received treatment following standard verbal consent without further investigations being performed.

Once eligibility had been established, baseline demographic and disease related information was obtained and a focused physical examination performed. Participants were then asked to complete the remainder of the baseline assessment of physical symptoms comprising the remainder of the WOMAC questionnaire and patient global VAS score. Next, participants were asked to complete the psychological questionnaires in the following order; IPQR, PCS, AIMS 2 depression subscale.
US scan of the index knee was performed according to the protocol described.

Following completion of the US examination, aspiration and injection of the index joint was performed as described (see section 4.8.1) together with assessment for air-arthrosonogram. Participants were advised to use a wheelchair to get to their transport and a period of 24 hours non-weight bearing rest was also advised. The total time for the baseline assessment, including consent and intervention, was around two hours.

**4.9.2 Follow-up**

A single follow-up appointment was conducted three weeks after treatment. Participants were asked to complete an outcome questionnaire composed of the WOMAC instrument and AIMS 2. At this visit participants were given a further outcome questionnaire, for completion and return in a stamped addressed envelope after a total of nine weeks after treatment. This questionnaire comprised the WOMAC and AIMS 2.

**4.10 Storage and handling of data**

Written documents containing patient identifiable data were stored securely within locked filing cabinets within the clinical research unit of Russells Hall hospital. Ultrasound images were stored on writable CDs and stored within the same facility. Study data not containing patient identifiable data were entered into a database using Microsoft Access using a secure computer terminal with password protection. Patients’ records were identified using a sequential study identifier, preserving anonymity of data and limiting patient identifiable data to date of birth only.

Accuracy of data entry was checked by rechecking 15 complete records from the access database against source data. Data was transferred from Access to SPSS via Excel, reshaping the data to produce a single record for each patient. Redundant fields were removed from the SPSS database and data was checked to ensure accurate
transfer of data. Data were examined using the explore command in SPSS as well as descriptive statistics to detect missing values or suspected data errors.

4.11 Analysis
4.11.1 Data processing

Analysis and data processing was conducted using Software Package for Social Sciences, version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Variable labels and missing data values were added. Subscale scores were calculated as appropriate. Missing data guidance for WOMAC index and IPQR was employed (250;251). This permits a given number of missing values for each subscale, dependent on the number of items in the subscale. In the case of missing values exceeding this limit, the whole subscale was considered to be invalid and a missing value recorded. The distribution of data was explored using descriptive statistics and histograms. Minimum and maximum values were checked to detect any missing or erroneous values and written source data examined as appropriate.

4.11.2 Imaging variables

From the ultrasound measurements, three US parameters were defined. Firstly, the mean effusion depth was calculated from triplicate measurements of effusion depth at each of the three sites of the SPP examined. This was done to try and create a measure representing the total volume of effusion, using the repeated measurements to compensate for any measurement error and three sites to compensate for heterogeneity of fluid accumulation within an OA knee joint. Secondly, mean synovial layer thickness was calculated in a similar manner by using the mean of the nine individual measurements (three for each of the mid, lateral and medial suprapatellar pouch. The power Doppler grade was applied as an ordinal variable with a range of 0-3, with the highest grade detected at any site being applied.

In relation to radiographs the maximum radiographic score for osteophyte (0-3) and joint space narrowing (0-3) at either compartment for each patient was used.
4.11.3 Interrelationship of psychological variables

The interrelationship of psychological factors was examined using a correlation matrix using Pearson’s correlation co-efficient. This was conducted to examine and confirm the strength of anticipated relationships between variables (for instance, the well documented and predicted relationships between IPQR variables) but also to identify any relationships sufficiently strong to raise concerns of co-linearity or variable redundancy prior to multivariable regression. Correlation coefficients of the order of 0.8 or greater are generally considered to constitute cause for concern regarding possible co-linearity.

4.11.4 Difference between primary and secondary OA

Baseline characteristics of patients with primary osteoarthritis were compared with those of participants with rheumatoid arthritis to examine for any significant baseline differences between groups. The test selected for this analysis was determined by the characteristics and distribution of data. Unpaired T tests were applied to normally distributed, continuous variables, Mann Whitney U tests to variables not normally distributed and Chi squared tests (or Fisher’s Exact test, as appropriate) for categorical variables.

4.11.5 Differences between responders and non-responders

Baseline characteristics of responders and non-responders at three and nine weeks were compared using appropriate statistical tests.

Logistic regression was performed on each of the factors found to be significant in the univariate analysis, entering the response status (separately at either 3 or 9 weeks) as the dependent variable in each case and the candidate predictor as the covariate. Separate logistic regression models were created for each of the psychological frameworks examined (illness perceptions, pain catastrophizing/depression). This approach was adopted as the most likely to generate a useful prediction model. For outcomes with more than one predictor multivariable logistic regression was conducted in a stepwise fashion using the forced entry method.
Models were adjusted for relevant baseline factors which were identified a-priori including diagnostic group (primary / secondary OA), baseline pain and whether the subject had received a previous injection.

Models were compared for goodness of fit by Hosmer-Lemeshow tests, comparison of model pseudo $r^2$ (Nagelkerke’s) and -2 Log Likelihood values and examination of residuals.

4.11.6 Planned interim analysis

A planned interim analysis occurred following the recruitment of the first 32 patients. This was conducted to test the study procedures and to refine study design if required, to detect any identifiable predictors or trends suggesting predictors of response and to inform the power calculation detailed in the following section. The interim analysis compared the characteristics of responders and non-responders at three and nine weeks.

4.12 Power calculation

The power calculation for our study is based on the interim analysis of the first 32 patients recruited and was performed by Mr Peter Nightingale, statistician at University Hospitals, Birmingham.

These data suggested that IPQR treatment control provided the best predictor of WOMAC response at three weeks and that the next closest relationship was IPQR consequences, although this was not itself significant as a predictor in the preliminary analysis. The power calculation aimed to determine the sample size necessary to detect an effect of IPQR consequences at three weeks in addition to the effect of treatment control.

The calculations were based on frequency of WOMAC response, defined as a WOMAC change score $>0.4$. The observed response rate in preliminary analysis was 53%. The observed mean for treatment control was 18.1 (SD 2.8.), consequences was 19.7 (SD 5.3) and the correlation between treatment control and consequences was -0.43. The
odds ratio for WOMAC response was 1.44 for treatment control and 0.98 for consequences in a multivariable logistic regression analysis including both variables. Based on an alpha 0.05 and power of 80% a sample size of 53 would be needed to detect a significant effect of treatment control in a univariate logistic regression. For multivariable logistic regression, a sample size of 200 was found to be sufficient to detect an odds ratio of 0.90 for consequences in a forward logistic regression model in which treatment control was entered first and consequences entered as the second variable, based on an alpha of 0.05 and a power of 80%. In order to allow for drop-out rate of 10% (higher than that observed in the pilot study) a recruitment target of 220 patients was set.

4.13 Ethical considerations

This study posed additional requirements of the participants beyond normal clinical care. These included a longer baseline appointment with ultrasound scan of the knee, the requirement to return for a short outcome assessment at three weeks and the requirement to complete the questionnaires. Screening and baseline procedures were completed immediately prior to the planned routine clinical treatment to avoid delaying it, as would have occurred with separate appointments.

One anticipated area for questions from the research ethics committee was of the potential hazard posed by the injection of small volume air in order to obtain an air arthrosonogram. As well as consideration of the hypothetical risks posed, this was assessed by a thorough search of associated literature using electronic databases, as well as articles describing the technique and citing articles (229;248). No report of any documented adverse event associated with the technique could be located. Although air embolism has been reported as a complication of arthrography or arthroscopy, these differ from our procedure in terms both of the very much larger volume of air injected (300ml in one report, (252)) and the higher pressures involved, both of which would increase the risk of this complication. Even so, the reported risk of air embolism even in these ‘higher risk’ procedures is rare at around 1/18000 to 1/20000 procedures. It was therefore estimated that mini air-arthrography conferred no
meaningful additional risks beyond that of a normal intra-articular injection that participants would be exposed to as part of standard care. The most serious risk of intra-articular steroid injection is infection, the risk of which is estimated to be 1/15000 or lower. More common but less severe problems include facial flushing, flare of pain and swelling in the injected knee, bruising and very occasionally bleeding. However, in the study patients had already agreed to have the injection as part of their routine clinical care.

Internal review of the overall study design and interventions was conducted internally within the sponsoring organization at the clinical site (Dudley Group NHS Foundation Trust). Following favourable opinion, formal application was made using the online Integrated Research Ethics System and submitted for review by the Local Research Ethics Committee, together with all documentation to be used in the study.

4.14 Timeline of REC permissions and patient recruitment

<table>
<thead>
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<th>Event</th>
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<tr>
<td>REC review of pilot phase</td>
<td>April 2011</td>
</tr>
<tr>
<td>REC approval pilot phase</td>
<td>May 2011</td>
</tr>
<tr>
<td>Recruitment pilot phase</td>
<td>May 2011- November 2011</td>
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<td>October 2012</td>
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<td>October 2012</td>
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<td>Recruitment continuation phase</td>
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Chapter Five:

Accuracy of injection and pain relief following intra-articular corticosteroid injection in knee osteoarthritis – an observational study

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Short Title: Accuracy of injection and pain relief

Key Words: intra-articular steroid injection, knee osteoarthritis, ultrasound, predictors of response
Abstract

Objective:
Intra-articular corticosteroid injections (IACI) are effective treatments for pain in knee OA but treatment response varies. There is uncertainty as to whether structural factors such as accurate placement of IACI affect outcome. We examined this question in a pragmatic observational study, using ultrasound (US) to verify accuracy of IACI.

Methods:
141 subjects with knee OA (mean age 63.4 years, 62% female) routinely referred for IACI underwent assessment of demographic factors, x-ray and US of the knee before aspiration and IACI (based on clinical landmarks) with 40 mg triamcinolone acetonide and lignocaine plus a small amount of atmospheric air by an independent physician. US demonstration of intra-articular mobile air, i.e. a positive air arthrosonogram, was used to determine accurate placement of injection. Both patients and injecting physicians were blind to the US findings. Pain at baseline, three and nine weeks post injection was assessed using the 500mm WOMAC pain subscale. Response to injection was defined as ≥ 40% reduction in pain from baseline. Characteristics of responders and non responders were compared using univariate statistics. Inter-observer reliability of air-arthrosonogram assessment was good: $\kappa$ 0.79 (three raters).

Results:
Mean baseline pain was 271 (SD 96.7) mm. 83 subjects (53%) were responders at three weeks and 56 (44%) at nine weeks. Ninety-eight subjects (70%) had a positive arthrosonogram. A positive air arthrosonogram neither associated with a higher rate of response to treatment ($p$ 0.355 at three weeks, $p$ 0.148 at nine weeks) nor with greater mean pain reduction compared to those with a negative air arthrosonogram (-110.7 mm vs -116.9 mm , $p$ 0.781 at three weeks, and -65.2 mm vs -92.8 mm, $p$ 0.247 at nine weeks).

There was no difference in US effusion depth, power Doppler signal or radiographic grade between responders and non responders to the injection.

Conclusions:
We found no evidence that accurate intra-articular injection of corticosteroid results in superior outcome in terms of pain compared to inaccurate injection in symptomatic knee OA.
Introduction

Osteoarthritis (OA) is the commonest form of arthritis worldwide and its prevalence is increasing (1). Knee osteoarthritis is one of the most common and disabling forms of the condition and has significant clinical and public health impact (2). In conjunction with other conservative measures to treat pain in knee OA, intra-articular corticosteroid injections (IACI) are commonly used in accordance with published guidance (3;4). Meta-analyses of placebo-controlled studies have confirmed that IACI provide effective pain relief for at least three weeks (5;6), with some studies suggesting effects of 14 weeks or more (6). There is considerable variation between individuals in both the magnitude and duration of response and identifying predictors of response to treatment has been suggested to be a priority for research in the field (5). Systematic reviews (7;8) of previous studies addressing the subject have found insufficient evidence of associations between radiographic grade (9;10) or clinical evidence of inflammation (10;11) and response to IACI. One potentially relevant, but so far insufficiently investigated factor that may plausibly govern response to IACI is accuracy of the injection. While the knee joint is perceived as being easy to inject with a high degree of accuracy, up to a third of routine injections based on anatomical landmarks may fail to enter the joint cavity (12;13); it remains unclear whether localisation of the steroid injection to within the knee joint cavity influences outcome.

The aim of this study was to determine whether accuracy of intra-articular placement of the injection, assessed by ultrasound, associates with improved outcome in terms of pain relief following routine IACI, based on clinical landmarks, in knee osteoarthritis.

Methods

Subjects

We studied a series of subjects with symptomatic knee OA who had been recommended by their treating physician to have an intra-articular steroid injection as part of their routine care. The setting was a single teaching district general hospital in the West Midlands of the UK. Potential participants were identified from orthopaedic and rheumatology clinics based in the hospital.

Men and women were eligible if they satisfied the following criteria: i) aged 40 years and over, ii) evidence of osteoarthritis of the knee according to ACR criteria (14), iii) baseline pain of 100/500 mm or higher on the WOMAC pain subscale, and iv) symptoms judged by the referring clinician as meriting IACI. Subjects with OA secondary to rheumatoid arthritis (RA) were also eligible, if a) their RA was considered to be inactive; b) they had knee symptoms of more than 6 weeks duration that were attributed to mechanical and not to inflammatory disease, and c) the x-ray of the index joint demonstrated radiographic changes of joint space narrowing and/ or osteophyte formation.

Subjects were excluded if they had received an intra-articular or intramuscular steroid injection within the preceding twelve weeks or were taking oral prednisolone at a dose of
7.5mg or higher or, a had a diagnosis of fibromyalgia or complex widespread pain, active RA or other inflammatory arthritis. The study was given external ethical approval (REC references 11/WM/0102 and 12/YH/0457) and all participants provided written informed consent.

**Baseline Assessment**
Subjects who consented to the study underwent baseline assessment, immediately prior to treatment. They completed an interviewer-assisted questionnaire which included information about their age, past medical history, and whether or not they had received previous knee injection. They also completed the WOMAC questionnaire (v3)(15). This uses five 100mm visual analogue scales (VAS) to assess knee pain and produces scores with a potential range of 0-500, with higher scores denoting higher levels of pain. Height and weight were assessed in a standard fashion. The baseline assessment also included psychological scales, the details of which will be reported elsewhere. Subjects had radiographs (antero-posterior, lateral and patellofemoral ‘skyline’ views) of their index knee unless already performed within the previous 6 months. High-sensitivity CRP (hsCRP) was measured using an enzyme immunoassay (MP Biomedicals, Solon, Ohio, US). Radiographs were graded by agreement by two observers (GH and RK), blinded to clinical details, using a standard atlas(16) which allows grading from 0 to 3 [0, normal; 3, severe changes] for individual features of osteophyte and joint space narrowing at both the tibiofemoral and patellofemoral joint(PFJ), including skyline views of the patellofemoral joint. In this grading system, grade 1 osteophyte is considered equivalent to Kellgren-Lawrence grade 2(16). The highest grade for each feature at any site was used for further analysis. In addition , subjects underwent ultrasound assessment with a 5-13 MHz linear US probe (VF13-5; Antares , Siemens Healthcare Diagnostics, Camberley, Surrey, UK) prior to injection for synovial effusion thickness and semi-quantitative synovial power Doppler signal estimation as described previously (17;18).

**Intervention**
The intervention was performed by one of several clinicians who were not involved with any of the other study procedures. Using their usual anatomical approach and injection technique, the clinician positioned the patient and they aspirated and injected the joint under aseptic precautions with a 21 G needle and a standard mixture of 40mg triamcinolone acetonide, 4ml 1% lignocaine and 2ml atmospheric air.

**Assessment of accuracy of intra-articular placement of injection**
The US probe was placed over the knee joint during the injection to determine placement of the injection. Air provides an effective US contrast medium through its features of being strongly hyperechoic, exhibiting posterior acoustic shadowing, buoyancy and mobility in fluid. We defined an accurate injection by the presence of a positive air arthrosonogram (see Figure 1), i.e. the presence of any mobile air visible within the joint cavity at the supra-patellar pouch. The technique was adapted from Qvistgaard et al (19) and applied as follows:
at the time of injection, the US probe was applied by GH to the midline suprapatellar pouch in the transverse plane and a video clip recorded. Immediately after the injection, a systematic US of all suprapatellar pouch areas was performed, starting at the site of injection in order to identify a positive air-arthrosonogram. Representative video clips were recorded, as was the sonographer’s immediate impression of whether air-arthrosonogram was present. A positive air-arthrosonogram at any of these sites was used for further analysis. The study subject and injecting clinician were not informed about the US findings. Following intervention, participants were advised to rest the joint as much as possible for 24 hours, in line with normal departmental practice.

**Assessment of response** Participants completed the WOMAC pain subscale at three and nine weeks post injection. We classified participants as responders at each time point, if their pain scores reduced by 40% or more from baseline, which has been estimated both a clinically important and perceptible change following intervention in knee OA(20)

**Analysis**

Descriptive statistics were used to summarise the subject characteristics. We determined at both 3 and 9 weeks whether subjects were responders or non-responders. We looked for differences in subject characteristics by response status at 3 and 9 weeks using t-tests or Mann Whitney U tests for continuous data and either Fisher’s exact test / Chi-Squared tests for categorical data. Inter-observer reliability of the air-arthrosonogram technique was calculated by presenting a sample of 26 stored video clips from the study to three observers (GH, AS, RK). An equal number of clips were selected from each set of originally classified as positive or negative air arthograms, respectively, at random. The studies were viewed in random order, independently by the observers scoring it as showing either positive or negative air-arthrosonogram. Inter-observer agreement was calculated for each pair of observers as a kappa value and the mean value calculated for the three pairs of observers. All analyses were conducted using SPSS version 20.

**Subjects**

A total of 141 patients were recruited to the study. Their mean age was 63.8 years and 87 (62%) were female. Mean BMI was 31 Kg/m$^2$. 105(74%) had primary OA and 36(26%) had secondary OA. Baseline pain level was 271 (SD 96.7)/500 mm. There were no significant differences in baseline characteristics between participants with primary and secondary OA except for hsCRP being higher in those with secondary OA (6.4 vs 4.4 mg/l, p=0.018) (Table 1). 140 subjects contributed outcome data at three weeks and 128 (91 %) at nine weeks. One participant submitted incomplete WOMAC pain scores at 3 weeks. Of the 13 participants who did not contribute to outcome data at nine weeks, one was withdrawn due
to an intercurrent episode of crystal arthritis, one questionnaire was lost in the post and 11 failed to return questionnaires. There were no statistically significant differences in baseline characteristics between those who did and did not complete the study (data not shown).

Accuracy of injection
Mean inter-observer agreement for air-arthrosonogram status was good, with mean kappa value between three raters of 0.79. 98 (69.5%) injections were considered to be accurate as determined by the presence of air on the arthrosonogram at the time of injection. There was no difference in accuracy of injection in those who had primary and those with secondary OA (70.5% vs 71.4%) (Table 1).

Response
The overall response rate was 59% at three weeks and 44% at nine weeks. Response rates were not statistically different in participants with primary vs secondary OA: 60.6 vs 55.6% at 3 weeks (p=0.69) and 45.7% vs 38.2% at 9 weeks (p=0.55) (Table 1).

Predictors of response
A positive arthrosonogram did not predict responder status at 3 or 9 weeks; in fact at both time points, response rates were higher in those with negative than those with positive arthrosonogram (75% vs 64.3%, p=0.148 at nine weeks) (Table 2). There were no statistically significant differences in baseline characteristics between responders and non-responders at three weeks. At nine weeks, non-responders were more likely to have had a previous IACI than non-responders (72% vs 52%; p=0.026) and a higher baseline pain score (288 vs 250 mm; p=0.031). A post-hoc analysis of absolute change in pain scores from baseline in groups with positive vs negative arthrosonogram showed no difference: -110.7 vs -116.9 mm, p 0.781 at three weeks; and -65.2 vs -92.8 mm, p 0.247 at nine weeks. Restricting analysis to those subjects with primary osteoarthritis did not alter the lack of association between accuracy and response to IACI (Table 3). It also showed a lower response rate at nine weeks in those who had received previous injections (p=0.021). Responders at three weeks were more likely to be female (p=0.045).

Discussion
In this prospective observational study we have shown that in knee osteoarthritis accurate intra-articular placement of a corticosteroid injection, as determined by positive air-arthrosonogram, did not improve the rate of clinically significant response or mean pain reduction, compared to extra-articular injection placement.

A recent systematic review (13) found that on average only 77% knee injections enter accurately the intra-articular cavity when using clinical landmarks as guidance for injection. It is therefore plausible to suggest that accuracy of injection may potentially explain the variability of response to IACI in knee OA. While there is little doubt that guidance by US improves accuracy of intra-articular placement of injection, there remains uncertainty as to
whether this affects outcome (13). In a small randomized study of 38 patients with knee OA, Sambrook et al found no difference in outcome between intentional intra-articular vs peri-patellar injection of methylprednisolone between one and twelve weeks post injection. This remains the only study that we are aware of that used clinical guidance of injection to address the role of intra- vs extra-articular corticosteroid injection in knee OA on outcome. The fact that no difference was observed in that study may have been due to the fact that correct intra-articular placement was not verified by further imaging (i.e. some intended intra-articular injections may still have ended up extra-articular) and/or lack of power (i.e. insufficient study sample) to show a difference. Sibbitt et al (21) examined the effect of ultrasound (US)-guidance vs – clinically guided IACI in a randomised study of 94 subjects with knee OA. No information on accuracy of the injection with either method is provided, but subjects undergoing US-guided injection were approximately twice as likely to have a positive response at 2 weeks (defined as a pain VAS of < 2cm). A second smaller study of essentially similar design by the same group showed similar findings. Both studies have not tried to control for any treatment effect likely to be conferred by the use of ultrasound itself, in other words: having an injection under ultrasound than without may have significant beneficial effect per se without any relationship to improved accuracy. That this is likely to be relevant is suggested by work by Cunnington et al (22) who used sham-US to compare US-guided injection vs clinically-guided injections in a variety of joints in a large study of 184 subjects with inflammatory arthritis: whilst, as expected US-guided injections were more accurate than clinically guided with sham-US, there was no difference in outcome (both pain and function) between the two groups. Furthermore, and more relevant to this study, function (but not pain) at 6 (but not 2) weeks was the only parameter that showed positive correlation with accuracy of injection. A trial studying US-guided vs ‘sham-US’ clinically-guided injection has been terminated and is to date unreported (ClinicalTrials.gov Identifier: NCT01032720; accessed 15 June 2015).

Our study showed further interesting observations: participants who had previous experience of injection were significantly less likely to report response to treatment than those undergoing their first injection at nine weeks (p 0.026), but not three weeks. This seems to concur with the anecdotal clinical observation that the effect of subsequent IACI in knee OA is less than of first injections. In line with most (11;23-25), but not all studies (9;10), we found no association between radiographic severity and rate of response, despite scoring separately for individual features of knee osteoarthritis. In accordance with other investigators (26;27), we found no relationship between response and sonographic effusion or synovial power Doppler, despite using a sonographic assessment that included measures from the medial, mid and lateral aspect of the supra-patellar pouch rather than single-view data.

The main strength of our study is that it was based on routine practice of IACI, using clinical guidance and subjects referred for IACI by their clinician as part of routine clinical management. It is possible that we may have seen better response rates than placebo-
controlled studies (5) due to contextual, non-specific treatment effects. It remains therefore possible that an adequately powered, placebo-controlled trial might disclose an effect of accuracy of injection on outcome. We did not undertake a formal sample size calculation; however, a post-hoc power calculation suggested that our recruited 141 patients would have provided sufficient power at 80% to detect a 30% relative difference between the WOMAC improvement of intra- vs extra-articular injection, assuming a SD of 20 mm (on a standardised 100 mm scale) in improvement with a ratio of 62 : 38 of intra-articular vs extra-articular injection. Although the rate of ‘successful’ intra-articular injection in our study was slightly higher at 70%, both the rates of reported response and mean pain reduction were higher at three and nine weeks in those participants in whom the injection failed to demonstrably reach the joint cavity. This makes it unlikely that even a substantial increase in sample size would show a superior effect of intra-articular injection. It is important to acknowledge that, in the absence of a formal power calculation for each somatic factor, we cannot be sure that the failure to detect associations between other factors such as radiographic grade or ultrasonographic evidence of inflammation and response was not the result of underpowering. However, the presence of effects that were clinically important, at least in terms of predicting response, seems questionable if they could not be detected in a sample of 141 patients.

The decision to recruit patients with knee OA secondary to rheumatoid arthritis was made pre-hoc because of anticipated difficulties to recruit a sufficient number of subjects with primary OA. This is obviously not ideal, but we took great care to assure that RA patients had quiescent disease, certainly as far as the index knee was concerned and all patients had at least joint space narrowing. Although high-sensitivity CRP in the serum was slightly higher in the OA subjects with RA, several observations would suggest that the recruitment of subjects with OA in the context of RA should not distract from the main finding of our trial: firstly the response rate was not different between those with ‘primary’ vs ‘RA-related’, secondary OA at 3 and 9 weeks; secondly there was no statistical difference in radiographic osteophyte grade score between the groups, and thirdly in 29% of patients the symptoms of knee OA preceded the symptoms of RA, indicating that many RA patients had primary-type OA accompanied by RA. Clearly, in order to allow a firmer conclusion about the role of accuracy of injection in knee OA (rather than knee arthritis in general) the results of a randomised study are required. Finally, we did not use a second imaging method (e.g. MRI or limited CT) to validate our method to verify accurate intra-articular injection. The presence of an air-arthrosonogram does not mean that 100% of the injectate entered the intra-articular space. Conversely, but arguably less likely, the absence of an air-arthrosonogram does not mean that all injectate has been placed extra-articularly. Good interobserver agreement suggests, however, that the sonographic method to judge mobile injectate within the joint cavity as present or not suggests that we have used a reliable method to judge accuracy. Furthermore, our accuracy data of 70% are broadly in line with those reported in a recent systematic review (13).
Our findings support the current practice of IACI in knee OA using clinical landmarks and palpation: this may lead to correct placement in about 70% of patients but there is no indication that accuracy of injection matters to outcome in terms of pain relief between 3 and 9 weeks. Whilst US may well have a treatment effect of its own and may well be useful to assist for aspiration or technically difficult injections, there is to date no convincing indication that the improved accuracy it confers to the injection matters to outcome of pain relief in this setting.

**Conclusion:**
We have shown in this ‘real-life’, observational study that IACI based on routine, clinically guided practice leads to relief of knee pain in osteoarthritis in the short- and medium-term, irrespective of whether injection placement can be demonstrated in the intra-articular space or not. This casts doubt over the relevance of accuracy of intra-articular injection placement to clinical outcome in this setting.

**Rheumatology Key Message:**
Accuracy of injection does not predict outcome following routine clinically guided intra-articular steroid injection in symptomatic knee osteoarthritis

**Funding:** The Dudley Group NHS Foundation Trust funded GH’s post to enable this study.

**Acknowledgements:** We thank Mr Tom Clare and Mr Matthew Waites, Consultant Orthopaedic Surgeons, and all medical Rheumatology Staff of DGH NHS FT for referring patients and performing injections for this study. We are also grateful to Mr Peter Nightingale, Wolfson Computer Laboratories, Queen Elizabeth Hospital, Birmingham, UK, for statistical advice.

**Disclosure statement:** The authors have declared no conflict of interest.
Reference List


Figure 1: A transverse ultrasound section of the mid supra-patellar pouch area of the right knee during injection, showing a positive air arthrosonogram: there is an emerging area of intra-articular air bubbles (arrows), initially faintly (A) and then more clearly visible (B), with posterior acoustic shadowing (*). Varying transducer pressure demonstrated the echogenic layer to be displaceable and display buoyancy, consistent with intra-articular placement of the injection.
Table 1: Baseline and response characteristics of study population and subgroups.

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<th>Characteristics</th>
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<th>Primary OA n=105</th>
<th>Secondary OA n=36</th>
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<tr>
<td>Age [years] [mean (SD)]</td>
<td>63.8 (11.1)</td>
<td>63.1 (11.3)</td>
<td>64.4 (10.9)</td>
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<td>Female [n (%)]</td>
<td>87 (62%)</td>
<td>62 (59%)</td>
<td>25 (69%)</td>
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<td>BMI [mean (SD)]</td>
<td>31.0 (6.3)</td>
<td>30.8 (5.5)</td>
<td>31.7 (8.3)</td>
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<td>Previous injection [ n (%)]</td>
<td>87 (62%)</td>
<td>60 (57%)</td>
<td>27 (75%)</td>
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<td>Baseline WOMAC Pain [mean(SD)]</td>
<td>271 (96.7)</td>
<td>266 (95.5)</td>
<td>288 (99.7)</td>
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<tr>
<td>US effusion depth [mm] [Mean (SD)]</td>
<td>3.66 (3.36)</td>
<td>3.74 (2.27)</td>
<td>3.38 (1.80)</td>
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<td>PD grade [median (IQR)]</td>
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<td>0 (0,1)</td>
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<td>Osteophyte grade [median (IQR)]</td>
<td>2 (1,3)</td>
<td>2(1,3)</td>
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<td>JSN grade [median (IQR)]</td>
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<td>2(1,2)</td>
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<tr>
<td>hs CRP [mg/L] [median (IQR)]</td>
<td>4.7 (2.0, 7.8)</td>
<td>4.4 (1.7,7.1)</td>
<td>6.4 (4.3, 8.9)</td>
<td><strong>0.018</strong></td>
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<td>Positive US arthrogram [n (%)]</td>
<td>99 (70.7%)</td>
<td>74 (70.5%)</td>
<td>25(71.4)</td>
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<td>Responders at 3 weeks [ n (%\textsuperscript{a})]</td>
<td>83 (59.3%)</td>
<td>63(60.6%)</td>
<td>20 (55.6%)</td>
<td>0.695</td>
</tr>
<tr>
<td>Responder at 9 weeks [n (%\textsuperscript{b})]</td>
<td>56(44.5 %)</td>
<td>43 (45.7%)</td>
<td>13(38.2%)</td>
<td>0.546</td>
</tr>
</tbody>
</table>

* comparing primary vs secondary OA (Fisher’s-exact-test for gender, previous injection, US arthrogram, responder status; t-test for age, BMI, baseline WOMAC pain, US effusion depth; Mann-Whitney U-test for PD grade and hsCRP; Chi-square test for osteophyte and JS narrowing grade. Abbreviations: BMI, body mass index; PD, power Doppler; JSN, joint space narrowing; hsCRP, high-sensitivity CRP.
Table 2: Baseline characteristics of responders vs non-responders at three and nine weeks

<table>
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<th>Characteristics</th>
<th>3 weeks (n=140)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Age [years [mean (SD)]</td>
<td>64.6 (10.6)</td>
<td>62.3 (11.6)</td>
<td>0.227</td>
<td>65.5 (11.1)</td>
<td>63.4 (11.4)</td>
<td>0.298</td>
</tr>
<tr>
<td>Female [n (%)]</td>
<td>55 (66%)</td>
<td>31 (54%)</td>
<td>0.163</td>
<td>40 (71%)</td>
<td>43 (60%)</td>
<td>0.194</td>
</tr>
<tr>
<td>BMI [mean(SD)]</td>
<td>31.1 (5.8)</td>
<td>30.9 (7.2)</td>
<td>0.856</td>
<td>30.9 (5.7)</td>
<td>31.1 (6.7)</td>
<td>0.808</td>
</tr>
<tr>
<td>Secondary OA [n (%)]</td>
<td>20 (24%)</td>
<td>16 (28%)</td>
<td>0.695</td>
<td>13 (23%)</td>
<td>21 (29%)</td>
<td>0.546</td>
</tr>
<tr>
<td>Previous injection [n (%)]</td>
<td>46 (55%)</td>
<td>40 (70%)</td>
<td>0.111</td>
<td>29 (52%)</td>
<td>52 (72%)</td>
<td>0.026</td>
</tr>
<tr>
<td>Baseline Pain [mean (SD)]</td>
<td>260 (91)</td>
<td>288 (103)</td>
<td>0.096</td>
<td>250 (95)</td>
<td>288 (99)</td>
<td>0.031</td>
</tr>
<tr>
<td>US effusion depth [mm][mean (SD)]</td>
<td>3.44 (2.0)</td>
<td>3.99 (2.4)</td>
<td>0.150</td>
<td>3.29 (1.9)</td>
<td>3.93 (2.41)</td>
<td>0.106</td>
</tr>
<tr>
<td>PD grade [median (IQR)]</td>
<td>0 (0,1)</td>
<td>1 (0,1)</td>
<td>0.071</td>
<td>0 (0,1)</td>
<td>0 (0,1)</td>
<td>0.170</td>
</tr>
<tr>
<td>Osteophyte grade [median (IQR)]</td>
<td>2 (1,3)</td>
<td>2 (1,3)</td>
<td>0.355</td>
<td>2 (1,2)</td>
<td>2 (1,3)</td>
<td>0.291</td>
</tr>
<tr>
<td>JSN grade [median (IQR)]</td>
<td>2 (1,2)</td>
<td>2 (1,2)</td>
<td>0.953</td>
<td>2 (1,2)</td>
<td>2 (1,2)</td>
<td>0.348</td>
</tr>
<tr>
<td>hsCRP [mg/L] [median (IQR)]</td>
<td>4.4 (1.9, 6.9)</td>
<td>6.2 (3.0,8.6)</td>
<td>0.073</td>
<td>3.5 (1.7, 6.5)</td>
<td>4.7 (2.2, 8.5)</td>
<td>0.141</td>
</tr>
<tr>
<td>Positive US arthrogram [n (%)]</td>
<td>56 (68.3%)</td>
<td>42 (73.7%)</td>
<td>0.355</td>
<td>36 (64.3%)</td>
<td>54 (75%)</td>
<td>0.148</td>
</tr>
</tbody>
</table>

* comparing primary vs secondary OA (Fisher’s-exact-test for gender, previous injection, US arthrogram, responder status; t-test for age, BMI, baseline WOMAC pain, US effusion depth; Mann-Whitney U-test for PD grade and hsCRP; Chi-square test for osteophyte and JS narrowing grade.

Abbreviations: BMI, body mass index; PD, power Doppler; JSN, joint space narrowing; hsCRP, high-sensitivity CRP.
Table 3: Baseline characteristics of responders vs non-responders at three and nine weeks; primary osteoarthritis subgroup

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>3 weeks</th>
<th>Non-responder</th>
<th>P</th>
<th>9 weeks</th>
<th>Non-Responder</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> [years [mean (SD)]**</td>
<td>64.4(10.6)</td>
<td>61.8(11.9)</td>
<td>0.258</td>
<td>64.1(11)</td>
<td>64.5(11)</td>
<td>0.890</td>
</tr>
<tr>
<td><strong>Female</strong> [n (%)]</td>
<td>42 (67%)</td>
<td>19 (46%)</td>
<td><strong>0.045</strong></td>
<td>31 (72%)</td>
<td>28 (55%)</td>
<td>0.093</td>
</tr>
<tr>
<td><strong>BMI</strong> [mean(SD)]</td>
<td>31.3(5.4)</td>
<td>30.0(5.8)</td>
<td>0.265</td>
<td>30.9(4.8)</td>
<td>30.4(5.8)</td>
<td>0.658</td>
</tr>
<tr>
<td><strong>Previous injection</strong> [n (%)]</td>
<td>33 (52%)</td>
<td>26 (63%)</td>
<td>0.314</td>
<td>20 (47%)</td>
<td>36 (71%)</td>
<td><strong>0.021</strong></td>
</tr>
<tr>
<td><strong>Baseline Pain</strong> [mean (SD)]</td>
<td>256(87)</td>
<td>279(107)</td>
<td>0.240</td>
<td>243(91)</td>
<td>282(99)</td>
<td>0.057</td>
</tr>
<tr>
<td><strong>US effusion depth</strong> [mm][mean(SD)]</td>
<td>3.57(2.1)</td>
<td>4.07(2.6)</td>
<td>0.280</td>
<td>3.29(1.9)</td>
<td>4.14(2.59)</td>
<td>0.080</td>
</tr>
<tr>
<td><strong>Mean synovial thickness</strong> [mm][Mean (SD)]</td>
<td>2.37(2.1)</td>
<td>2.63(2.4)</td>
<td>0.573</td>
<td>2.11(1.9)</td>
<td>2.88(2.5)</td>
<td>0.160</td>
</tr>
<tr>
<td><strong>Osteophyte grade</strong> [median (IQR)]</td>
<td>2(1,3)</td>
<td>2(1,3)</td>
<td>0.870</td>
<td>2(1,2)</td>
<td>2(1,3)</td>
<td>0.540</td>
</tr>
<tr>
<td><strong>JSN grade</strong> [median (IQR)]</td>
<td>2(1,2)</td>
<td>2(1,2)</td>
<td>0.796</td>
<td>2(1,2)</td>
<td>2(1,2)</td>
<td>0.461</td>
</tr>
<tr>
<td><strong>PD grade</strong> [median (IQR)]</td>
<td>0(0,1)</td>
<td>0(0,1)</td>
<td>0.790</td>
<td>0(0,1)</td>
<td>0(0,1)</td>
<td>0.376</td>
</tr>
<tr>
<td><strong>Positive US arthrogram</strong> [n (%)]</td>
<td>42 (67%)</td>
<td>30 (73%)</td>
<td>0.389</td>
<td>27 (64%)</td>
<td>38 (75%)</td>
<td>0.365</td>
</tr>
<tr>
<td><strong>hsCRP</strong> [mg/L][median (IQR)]</td>
<td>3.5(1.5,6.8)</td>
<td>4.6(2.2,8.6)</td>
<td>0.147</td>
<td>3.0(1.5,5.7)</td>
<td>4.5(1.7,8.6)</td>
<td>0.857</td>
</tr>
</tbody>
</table>

* comparing primary vs secondary OA (Fisher’s-exact-test for gender, previous injection, US arthrogram, responder status; t-test for age, BMI, baseline WOMAC pain, US effusion depth; Mann-Whitney U-test for PD grade and hsCRP; Chi-square test for osteophyte and JS narrowing grade.
Abbreviations: BMI, body mass index; PD, power Doppler; JSN, joint space narrowing; hsCRP, high-sensitivity CRP.
Chapter Six:

Illness Perceptions and depression predict response to intra-articular steroid treatment in symptomatic knee osteoarthritis.

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Illness Perceptions and depression predict response to intra-articular steroid treatment in symptomatic knee osteoarthritis.

G. Hirsch, T. O’Neill, J.Duda, R.Klocke

Abstract

Background: Intra-articular corticosteroid injections (IACI) are a commonly used and effective treatment for pain in knee osteoarthritis. Individual responses to treatment vary but the factors governing this variation are still not known. Psychological factors including illness perceptions and pain catastrophizing have been shown to influence the outcome of arthroplasty but their ability to predict outcome following IACI has not been tested.

Objectives: To determine whether patient-reported illness perceptions, depression and pain catastrophizing predict outcome of pain following IACI in patients with symptomatic knee osteoarthritis.

Methods: Consenting patients with symptomatic painful knee OA received IACI (40 mg triamcinolone acetate plus 4 ml 1% lignocaine) as part of standard clinical care. Baseline assessments conducted prior to injection included patient characteristics, assessment of pain using WOMAC and psychological questionnaires including the Revised Illness Perception Questionnaire (IPQR), Pain Catastrophizing Scale and depression subscale of the revised Arthritis Impact Measurement Scale prior injection. Outcome was assessed at three and nine weeks, with response to treatment being defined as a minimum 40% decrease of pain from baseline. Characteristics of responders and non-responders were compared and factors significant in univariable analysis were entered into multivariable logistic regression, incorporating adjustment for anticipated confounders. Separate models were constructed for IPQR variables and pain catastrophizing/depression.

Results: 141 subjects were recruited. Mean age was 63.8 and 62% were female. 36 (26%) subjects had radiographic knee OA in the context of quiescent rheumatoid arthritis. 83 subjects (59%) were classified as responders at 3 weeks and 56 (44%) at 9 weeks. Predictors of response: (i) IPQR variables: Higher treatment control was the only independent predictor of response to treatment at three weeks (Odds Ratio (OR) 1.21 [1.05-1.40]). At nine weeks, independent predictors of response to treatment were higher treatment control (OR 1.24[1.05-1.47]) and lower consequences (OR 0.83[0.75-0.93]) (ii) Depression and Pain Catastrophizing: Higher depression predicted non-response to treatment at nine weeks (OR 0.86[0.75-0.99]). Neither variable was an independent predictor of outcome at three weeks.

Conclusions: In this first detailed examination of the effect of psychological factors on the outcome of intra-articular corticosteroid injection in knee osteoarthritis, baseline Illness perceptions, specifically the domains treatment control and consequences, as well as depression predicted the outcome of treatment at nine weeks.
Introduction

Symptomatic knee osteoarthritis affects one in eight men and women and is linked with significant morbidity and functional impairment. In the absence of disease modifying treatments to prevent or retard the progression of OA (1), current management is focused on reducing symptoms and improving function. Intra-articular Corticosteroid injections (IACI) are recommended for use in both national and international guidelines for management of osteoarthritis (2;3). Systematic reviews have confirmed their effectiveness in relieving pain (4), although up to 30% of patients do not respond and of those who do there is variation in the duration of response. Previous studies have identified no consistent structural or disease specific factors which influence response (5;6). However there are few data which have looked at psychosocial factors (7) and none examining illness perceptions or pain catastrophizing.

Growing evidence suggests a role for illness perceptions (IPs) as important predictors of outcome in osteoarthritis (8-14) as well as other chronic conditions(15;16). IPs are a set of congruent beliefs that an individual forms with respect to a specific illness. They comprise discrete domains including beliefs about how long an illness is likely to continue (timeline), its perceived impact (consequences), the degree to which the illness or its symptoms may be controlled(control beliefs) the emotional response to the condition (emotional representations), understanding of the illness (coherence) and the number of symptoms attributed to it (identity). According to the Common Sense Model (17), IPs are formed in response to disparate influences including direct experience, available information and emotional processes. IPs then determine the coping strategies adopted in response to the illness. Lastly, the effectiveness of such strategies is evaluated and IPs revised in light of this. Patterns of IPs held by individuals reflect logical inter-relationships; for instance beliefs in chronic timeline are usually associated with perceptions of severe adverse consequences and low perceptions of control. Thus while domains are measured individually, they represent interacting elements of a coherent whole. With respect to clinical outcomes in the case of OA, it has been shown that baseline IPs in individuals with lower limb OA predict disability at six years(10), outcome following arthroplasty (8;12-14) and outcomes of rehabilitation (18).

There are though no data looking at their potential impact on response to pharmacological therapies.

Pain catastrophizing describes a “highly negative emotional set in response to real or imagined pain” (19). A meta-analysis concluded that there is strong evidence for its role as an independent predictor of poor outcomes following knee arthroplasty (20). Again, there are no data looking at its potential impact on outcome following knee injection.

We hypothesised that those with negative profiles of illness perceptions (in particular low scores for treatment control and personal control, indicating lower perceptions of control over the symptoms or course of disease by medical treatment or personal action and higher scores for consequences and timeline, denoting higher perceived impact of illness on the individual and more chronic timeline) and greater tendencies toward pain catastrophizing would be less likely to respond to IACI in terms of pain relief. To look at this we studied a series of men and women with symptomatic knee OA who received an intra-articular steroid injection as part of their routine clinical care and aimed to determine the role of IPs and pain catastrophizing in predicting response to therapy.
Methods

Subjects

Men and women aged 40 years and over with symptomatic primary or secondary OA and who had been recommended for therapy with intra-articular steroid injection by their physician were recruited for participation in an observational study looking at treatment response. The setting was a single district general teaching hospital in the West Midlands region of England. Participants were recruited from orthopaedic and rheumatology clinics within the hospital. Subjects received information about the study and all provided written informed consent. The study was subjected to independent ethical review and given approval (REC references 11/WM/0102 and 12/YH/0457).

Inclusion/Exclusion criteria

Subjects were included if they had primary osteoarthritis of the knee according to ACR criteria (21), had baseline score of 100/500 mm or higher on the WOMAC pain subscale and that their symptoms were judged by the referring clinician as being sufficiently severe to warrant intra-articular corticosteroid injection. We included also subjects with these pain criteria and OA secondary to rheumatoid arthritis which the referring clinician judged to be well controlled, who had knee symptoms of more than 6 weeks duration that were attributed to mechanical rather than inflammatory causes and an x-ray of the index joint that demonstrated radiographic changes compatible with osteoarthritis.

Subjects were excluded if they had any contraindication to IACI, had received an intra-articular or intramuscular steroid injection within the preceding twelve weeks, were taking oral prednisolone at a dose of 7.5mg or higher or had a diagnosis of fibromyalgia or chronic widespread pain.

Assessments

Subjects completed a baseline assessment prior to aspiration and injection of the index joint. The assessment included information about personal and medical history, information about their condition including duration of symptoms, and any history of previous injections (together with a visual analogue score [VAS] score for recalled effectiveness). Subjects were examined clinically for the presence of effusion. Height and weight were recorded in a standard fashion. In addition they completed a number of questionnaires, had ultrasound of the knee performed and gave a blood sample for measurement of high sensitivity CRP (hsCRP). Those who had not had prior knee radiographs in the previous 6 months had further radiographs performed. Details of these assessments are outlined below:

i) Questionnaires

Psychological questionnaires competed at baseline included the revised Illness Perception Questionnaire (IPQR) (22), Pain Catastrophizing Scale (PCS) (23) and depression subscale of the Arthritis Impact Measurement Scale (AIMS2) instrument (24). All have measurement properties (internal consistency, reliability, responsiveness) ranging from good to excellent in OA (24-26).

The IPQR is a standard instrument for measuring illness perceptions comprising 38 questions organised into 7 distinct domains as well as separate scales for illness identity and causes. The wording of the IPQR questionnaire used was for knee arthritis, as suggested by the authors.
The scales of particular interest were the Treatment Control domain (range 5-25, where higher scores denote stronger beliefs that treatment can alter the course or symptoms of an illness), Personal Control (range 6-30, where high scores denote greater belief in the effects of personal actions on outcome) and Consequences (range 6-30, where higher scores denote greater perceived impact of the condition on the individual’s lifestyle and activities). The PCS is the instrument most commonly used for measuring pain catastrophizing. It comprises 13 questions, each answered with a Likert scale graded 0-4 and gives a possible score range of 0-52, with higher scores indicating greater tendency to pain catastrophizing. The depression subscale of the AIMS 2 comprises 5 questions, answered in Likert format, where possible score range from 5-25 (where 25 indicates most severe symptoms of depression.) Pain was assessed prior to injection using the WOMAC index (version 3) (27). This comprises five questions relating to pain suffered in the index joint over the preceding 48 hours, answered using 100mm visual analogue scales.

ii) Radiographs
AP, lateral and skyline radiographs were acquired of the index joint according to a standard hospital protocol, unless adequate radiographs had been acquired in the preceding six months. Radiographs were graded by two observers (GH and RK) using a standard atlas (28). Features of osteophyte and joint space narrowing were graded separately (0-3) for the tibiofemoral and patellofemoral compartments and independently by each observer. The highest grade for each feature for either compartment was used in analysis, with consensus between observers being reached in case of disagreements.

iii) Ultrasound
In addition to clinical examination of the index joint, all subjects underwent detailed ultrasound examination of the suprapatella pouch (as described in (29), including measurement of both effusion and synovial hypertrophy. The details of this examination and their relation to outcome are reported in detail in another manuscript. Findings or interpretations of the US examination were not shared with patients or clinicians in order to avoid bias.

iv) hsCRP sample
A single 5ml blood sample was drawn from consenting patients for measurement of hsCRP.

Intervention
Aspiration and injection of the index joint was performed by an independent clinician not connected with study assessments, guided by clinical examination and using their usual preferred approach and technique. Under aseptic precautions the index joint was aspirated to dryness using a 21 gauge needle and injected with a standard mixture of 40mg triamcinolone and lignocaine 4ml 1%.

Follow up
Participants were seen again after 3 weeks when they were asked to complete the WOMAC questionnaire. At this visit they were also given a further questionnaire (WOMAC) and asked to complete this 9 weeks post injection and return by post. Response to injection was defined at each time-point as a minimum 40% reduction in pain from baseline to follow-up, a definition chosen since it has been estimated to be the minimum clinically meaningful improvement to patients (30).
**Statistical analysis**

Descriptive statistics were used to characterise subject characteristics. Differences between responders and non-responders at both 3 and 9 weeks was assessed using t-tests and Mann-Whitney tests for continuous data and Chi Squared test for categorical variables. Those variables linked to response in univariate analysis (using the threshold of p<0.05) were entered into multivariate logistic regression models, with treatment response as the outcome and the results expressed as odds ratios and 95% confidence intervals.

Separate models were constructed based on IPs and depression/pain catastrophizing, reflecting the different psychological frameworks in which they operate. In these analyses adjustments were made for putative confounders including diagnostic group (primary / secondary OA), baseline pain and whether subjects had received previous injections. Nagelkerke’s pseudo $r^2$, an estimate of the proportion of variance in probability of response determined by each model, was used as a further measure of effect size for the whole model.

Statistical analysis was conducted using SPSS v20.

**Results**

**Subjects**

141 patients were recruited to the study. 140 contributed outcome data at three weeks and 128 outcome data at nine weeks. One participant failed to provide complete outcome data at three weeks. Of the 13 participants who did not return outcome data at nine weeks, one had been withdrawn as he had an attack of crystal arthritis, one submitted a questionnaire which was lost in the post and 11 failed to return the postal questionnaires. The mean age of the 141 subjects was 63.8 years and 62% were female. 105 (74%) of these had primary OA, see Table 1. There were no statistical differences in baseline characteristics between those 128 subjects who did and 13 who did not complete the study. There were no differences also in any of the baseline characteristics between those with primary and secondary OA, with the exception of a higher hSCRP value in those with secondary OA (6.4 vs 4.4, P 0.018).

**Response**

83 (59%) participants were classified as responders at three weeks and 56 (44%) participants were responders at nine weeks.

**Univariate analysis**

i) Subject characteristics

There were no significant differences in baseline subject characteristics between responder and non-responders at three weeks (data not shown). At nine weeks, baseline pain scores were lower in responders than non-responders (mean scores 250 vs 288, p=0.031). Previous injection treatment was associated with a lower rate of response at nine weeks to the treatment in the study (35.8 % vs 57.4%; p=0.026).

ii) IPQR variables

Responders at three weeks were found to have significantly higher scores for IPQR treatment control domain (18.90 vs 17.36; p=0.001) and lower scores for IPQR consequences (19.10 vs 21.80; p=0.005) than non responders (see Table 2). There were trends towards responders
having lower scores for IPQR timeline (23.06 vs 24.54; p=0.054) and higher scores for IPQR personal control (21.30 vs 19.78; p=0.087) than non-responders.

At nine weeks, responders had significantly higher scores for treatment control (19.40 vs 17.64; p=0.002) and lower scores for consequences (17.60 vs 21.91; p<0.001) and emotional representations (15.73 vs 18.18; p=0.012) than non-responders.

iii) Pain catastrophizing

Responders had lower scores for depression (9.98 vs 12.02; p=0.001) and pain catastrophizing (13.89 vs 21.35; p=0.005) than non responders at three weeks, and also at nine weeks (9.19 vs 12.24; p<0.001 and 11.16 vs 20.74 p=0.001 respectively.)

**Multivariate analysis**

Separate multivariable models of outcome at three and nine weeks were constructed for each group of psychological factors examined (IPQR variables and depression/ pain catastrophizing). These were adjusted for baseline pain and whether subjects had received previous injection as well as diagnostic group (primary OA/ secondary OA).

i) IPQR variables

In a multivariate model of outcome at three weeks based on IPQR variables (treatment control and consequences), higher treatment control was the only independent predictor of response retained in the adjusted model (OR=1.21; 95%CI 1.05, 1.40). This indicates that subjects who held stronger beliefs that treatment could influence the symptoms or outcome of their illness were more likely to respond to treatment. The model predicted outcome at three weeks (p=0.003) with a total model $r^2$ of 0.17 (see Table 3).

An adjusted model of outcome at nine weeks (see Table 4) containing the IPQR domains treatment control, consequences and emotional representations was highly significant (p<0.001) and $r^2$ was 0.30. Consequences and treatment control were found to contribute independently to the model (p 0.001, OR=0.83; p 0.001 and OR=1.27 respectively), with lower scores for consequences and higher scores for treatment control being linked with response. This indicates that subjects who held stronger beliefs that treatment could help their condition and perceived less serious effects of their arthritis on their lives overall were more likely to respond to treatment. Emotional representations did not reach independent significance (p=0.847).

ii) Depression and pain catastrophizing

A multivariate model of outcome at three weeks based on depression and pain catastrophizing predicted outcome (p=0.015, $r^2 =$0.13). However, neither factor was an independent predictor of outcome, although there was a trend in favour of higher depression predicting non-response (p=0.065).

In the nine week regression model containing depression and pain catastrophizing, higher depression was an independent predictor of non-response (p=0.034), whereas pain catastrophizing was not (p=0.141). The overall model was significant (p=0.001) and $r^2$ was 0.20.
Restricting analysis to those with primary osteoarthritis, at three weeks the model was significant but no independent predictors remained after personal control was included in the model, see Tables 5 and 6. At nine weeks, the same independent predictors of response were identified, but with a larger model \( r^2 (0.42) \), suggesting that a higher level of variance could be explained by the model than in the whole sample.

**Discussion**

In this study illness perceptions, and in particular treatment control and consequences, predicted outcome following intra-articular corticosteroid injection in symptomatic knee osteoarthritis. Those with a more negative view of their arthritis; those perceiving greater adverse on their lives and of their arthritis as being less amenable to treatment, were less likely to report a significant improvement in their pain after three weeks and, to a greater extent, after nine weeks. Higher scores for depression predicted non-response to treatment at nine weeks independent of pain catastrophizing. Contrary to our expectations, pain catastrophizing was not found to predict response independent of depression. By contrast, we found no significant evidence to support an influence of baseline physical factors (such as age, BMI or radiographic severity) in predicting response to IACI. These findings are reported in detail in a further manuscript.

To the best of our knowledge we are not aware of published studies that have examined IPs and pain catastrophizing in the context of IACI. Our data are though consistent with studies in knee OA looking at the effect of IPs on outcome following surgical intervention. Orbell first observed a relationship between IPs and outcome of arthroplasty, demonstrating that stronger control perceptions predicted greater improvement in function at nine months post surgery(12). Bethge found that higher treatment control predicted greater reduction in pain following total hip replacement, moderated by the level of concern they had about illness (a domain not present in the IPQR but showing high correlation with consequences)(13). Hanusch did not find any IPQR domains to be unique predictors of variance in Oxford knee score(OKS) at six weeks post surgery but that model containing consequences and coherence explained 7.9% of variance in OKS score(14). Pinto found perception of more chronic timeline to be the sole independent predictor of severe postsurgical pain at six months post knee arthroplasty.

With respect to pain catastrophizing and depression, in contrast to what we had expected, both factors were found to be associated with response status in univariate analysis but neither emerged as an independent predictor of response at three weeks, while depression predicted outcome at nine weeks, independent of pain catastrophizing. This is in contrast to several previous published studies, in which higher pain catastrophizing predicted poorer pain outcomes post arthroplasty, independent of depression(31;32). However, our results are consistent with those of Edwards, in which depression was found to predict pain post TKR independent of pain catastrophizing.(33). The reason for these differences is unclear.

In the case of effusion and radiographic grade, previous studies have demonstrated such relationships although not consistently, nor at more than one time point in each case (34-36). We found an association between higher response rates at nine weeks with lower baseline
pain and having no previous experience of injection. There was also an association between female gender and higher response rate at three weeks but only in the subset of subjects with primary OA. These variables were included in regression analysis for the OA subset but were not significant in the final models.

We found that previous experience of injection predicted a lower rate of response at nine weeks. The effect of previous injection was no longer significant in a logistic regression model containing IPs, suggesting that IPs may explain at least some of the relationship. A previous longitudinal study of IPs in OA showed that IPs in some patients become more negative over time(11). This could result in a lower probability of response to IACI over time, although disease duration did not predict response to treatment in the sample we observed.

**How might illness perceptions impact on response to IACI?**

According to the Common Sense Model, illness perceptions influence the choice of coping strategies employed by an individual and that these mediate the effect of IPs on outcome. Coping strategies may take many forms but some simple examples in this context might include use of analgesia (as might be encouraged by stronger control perceptions), exercise and activity pacing (as might be reduced by severe perceived consequences) as well as cognitive strategies such as distraction and reinterpretation of pain, as opposed to ‘maladaptive coping strategies such as activity avoidance or passive pacing. The role of coping strategies in mediating illness perceptions remains only partially proven (37;38). This may in part be due to the use of relatively insensitive tools to measure what are complex and varied processes, but also that the effectiveness of a coping strategy may differ according to the situation(39). It is likely that other mechanisms might account for some of the effect of illness perceptions on clinical outcomes. One possibility is through the activation of endogenous opioid pathways, which have been shown to mediate the placebo effect relating to expectation of analgesia (40;41) and to be impaired in pain catastrophizing (42).

There are a number of limitations which need to be considered in interpreting data from this study. Subjects were recruited from a secondary care setting and so may not necessarily be generalised to a primary care setting for which further data is needed. Analgesic use was not restricted or recorded during the course of this observational study. We included participants with both primary and radiographic OA in the context of quiescent rheumatoid arthritis (here termed secondary OA). We asked participants with RA to complete the IPQR with reference to their knee problem as opposed to their RA in general but we cannot exclude an influence on their scores, although we found no systematic, statistically significant differences from those with primary OA. 13 participants were lost to follow-up at nine weeks, which represents a rate of 9%. It is possible that this may have impacted on outcome if these subjects were more or less likely to be responders at 9 weeks than those who continued to take part. Since there were no significant differences either in baseline characteristics or in response rate at three weeks between those who did and did not complete the study, we do not believe that our results would have been different had there been no loss to follow.
What are the implications of our findings?

Identifying predictors of response to treatment can provide insight into the mechanisms governing treatment effects and may also enable targeted treatment. Identification of modifiable factors governing response, however, could offer the potential to improve treatment outcomes. Many psychological factors are considered to be ‘state’ characteristics that may change or be modified. IPs, as defined in the CSM, are dynamic. Interventions to alter IPs to a more favourable profile have been demonstrated to be effective in the context of chronic lung disease, diabetes, chronic pain and multiple sclerosis (43-46). In most cases, these changes are accompanied by improved clinical outcomes. Whether this is the case for OA and response to IACI will require further investigation. Our findings add to a growing literature demonstrating IPs to be important determinants of clinical outcomes in OA. This further strengthens the argument both for this framework to be considered in the education of patients with osteoarthritis (47) and for the creation and implementation of specific, targeted interventions designed to challenge negative perceptions of illness with the aim of improving treatment outcomes.

In summary illness perceptions, specifically perceptions of the consequences of disease for the individual and of the effectiveness of treatment, and depression predict clinical response to intra-articular corticosteroid injection in knee osteoarthritis.

Acknowledgements: We are grateful to Mr T. Clare, Mr M. Waites and Dr G. Parsons for assistance with recruitment to the study and to Drs A.V. Pace, R. Sandhu and Dr T. Dimitroulas, who performed injections. The work was funded by an unrestricted educational grant from Dudley Group NHS Foundation Trust.
Reference List


Table 1: Baseline characteristics of study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>36 (26)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Female</td>
<td>87 (62)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Clinical Effusion</td>
<td>39 (28)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Previous injection</td>
<td>87 (62)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
<td>-</td>
<td>63.8 (11.2)</td>
<td>-</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>-</td>
<td>31 (6.3)</td>
<td>-</td>
</tr>
<tr>
<td>Duration symptoms/ months</td>
<td>-</td>
<td>76 (87)</td>
<td>-</td>
</tr>
<tr>
<td>Maximum osteophyte grade</td>
<td>-</td>
<td>-</td>
<td>2 (1,3)</td>
</tr>
<tr>
<td>Maximum JSN grade</td>
<td>-</td>
<td>-</td>
<td>2 (1,2)</td>
</tr>
<tr>
<td>Baseline Pain (WOMAC)</td>
<td>-</td>
<td>271 (97)</td>
<td>-</td>
</tr>
<tr>
<td>Timeline Chronic (IPQR)</td>
<td>-</td>
<td>23.6 (4.4)</td>
<td>-</td>
</tr>
<tr>
<td>Timeline Cyclical (IPQR)</td>
<td>-</td>
<td>14.1 (3.8)</td>
<td>-</td>
</tr>
<tr>
<td>Consequences (IPQR)</td>
<td>-</td>
<td>20.3 (4.9)</td>
<td>-</td>
</tr>
<tr>
<td>Personal control (IPQR)</td>
<td>-</td>
<td>20.7 (3.6)</td>
<td>-</td>
</tr>
<tr>
<td>Treatment Control (IPQR)</td>
<td>-</td>
<td>18.2 (2.8)</td>
<td>-</td>
</tr>
<tr>
<td>Coherence (IPQR)</td>
<td>-</td>
<td>17.9 (4.1)</td>
<td>-</td>
</tr>
<tr>
<td>Emotional Representations (IPQR)</td>
<td>-</td>
<td>17.2 (5.1)</td>
<td>-</td>
</tr>
<tr>
<td>Identity (IPQR)</td>
<td>-</td>
<td>4.1 (1.8)</td>
<td>-</td>
</tr>
<tr>
<td>Depression (AIMS2)</td>
<td>-</td>
<td>10.9 (3.7)</td>
<td>-</td>
</tr>
<tr>
<td>Pain Catastrophizing (PCS)</td>
<td>-</td>
<td>17 (13.9)</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 2: Characteristics of responders and non-responders at three and nine weeks

<table>
<thead>
<tr>
<th>Baseline Factor</th>
<th>Week 3</th>
<th>Week 9</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-responder (n=57)</td>
<td>Responder (n=83)</td>
<td>Mean difference/ (SE)</td>
<td>P</td>
<td>Non-responder (n=72)</td>
<td>Responder (n=56)</td>
<td>Mean difference/ (SE)</td>
<td>P</td>
</tr>
<tr>
<td>Timeline(IPQR)</td>
<td>24.54</td>
<td>23.04</td>
<td>1.46 (0.75)</td>
<td>0.054</td>
<td>23.99</td>
<td>22.69</td>
<td>1.29(0.80)</td>
<td>0.107</td>
</tr>
<tr>
<td>TimeCyclical (IPQR)</td>
<td>14.02</td>
<td>14.10</td>
<td>-0.07 (0.66)</td>
<td>0.905</td>
<td>14.38</td>
<td>13.68</td>
<td>0.70(0.66)</td>
<td>0.296</td>
</tr>
<tr>
<td>Consequences (IPQR)</td>
<td>21.70</td>
<td>19.37</td>
<td>2.33 (0.83)</td>
<td><strong>0.005</strong></td>
<td>21.93</td>
<td>17.94</td>
<td>3.99(0.80)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Personal Control (IPQR)</td>
<td>20.05</td>
<td>21.10</td>
<td>-1.06 (0.61)</td>
<td>0.087</td>
<td>20.36</td>
<td>21.26</td>
<td>-0.90(0.62)</td>
<td>0.150</td>
</tr>
<tr>
<td>Treatment Control (IPQR)</td>
<td>17.31</td>
<td>18.83</td>
<td>-1.52 (0.46)</td>
<td><strong>0.001</strong></td>
<td>17.64</td>
<td>19.12</td>
<td>-1.48(0.46)</td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>Coherence (IPQR)</td>
<td>17.96</td>
<td>17.97</td>
<td>-0.01 (0.72)</td>
<td>0.986</td>
<td>17.95</td>
<td>17.73</td>
<td>0.22(0.78)</td>
<td>0.774</td>
</tr>
<tr>
<td>Emotional Representations(IPQR)</td>
<td>17.79</td>
<td>16.97</td>
<td>1.02 (0.88)</td>
<td>0.245</td>
<td>18.16</td>
<td>15.96</td>
<td>2.19(0.86)</td>
<td><strong>0.012</strong></td>
</tr>
<tr>
<td>Pain Catastrophizing (PCS)</td>
<td>21.13</td>
<td>14.37</td>
<td>6.80 (2.35)</td>
<td><strong>0.005</strong></td>
<td>20.43</td>
<td>12.27</td>
<td>8.16(2.35)</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Depression (AIMS2)</td>
<td>12.13</td>
<td>10.00</td>
<td>2.13 (0.61)</td>
<td><strong>0.001</strong></td>
<td>11.99</td>
<td>9.50</td>
<td>2.45(0.62)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
</tbody>
</table>
Table 3: Predictors of early response (3 weeks); logistic regression

<table>
<thead>
<tr>
<th>Model</th>
<th>P value</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>R²</th>
<th>P value</th>
<th>Odds Ratio (final model)</th>
<th>95% Confidence Interval</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1) Model based on IPQR variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consequences (IPQR)</td>
<td>0.007</td>
<td>0.90</td>
<td>0.84-0.97</td>
<td>0.07</td>
<td>0.105</td>
<td>0.93</td>
<td>0.86-1.01</td>
<td>0.17</td>
</tr>
<tr>
<td>Treatment Control (IPQR)</td>
<td>0.002</td>
<td>1.25</td>
<td>1.08-1.43</td>
<td>0.10</td>
<td><strong>0.010</strong></td>
<td>1.21</td>
<td>1.05-1.40</td>
<td></td>
</tr>
<tr>
<td><strong>2) Model based on PCS/depression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression (AIMS2)</td>
<td>0.001</td>
<td>0.84</td>
<td>0.76-0.94</td>
<td>0.11</td>
<td>0.065</td>
<td>0.88</td>
<td>0.78-1.01</td>
<td>0.13</td>
</tr>
<tr>
<td>Pain Catastrophizing (PCS)</td>
<td><strong>0.006</strong></td>
<td>0.97</td>
<td>0.94-0.99</td>
<td>0.08</td>
<td>0.279</td>
<td>0.98</td>
<td>0.95-1.02</td>
<td></td>
</tr>
</tbody>
</table>

*Multivariable logistic regression analysis adjusted for baseline pain, diagnosis (RA/OA), and whether patients have undergone previous injection.

Models based on IPQR and PCS/depression were constructed independently and were not mutually adjusted.
### Table 4: Predictors of response at nine weeks; logistic regression.

<table>
<thead>
<tr>
<th></th>
<th>Univariable analysis</th>
<th></th>
<th>Multivariable analysis, adjusted*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P value</td>
<td>Odds Ratio</td>
<td>95% Confidence Interval</td>
<td>R²</td>
</tr>
<tr>
<td>1) Model based on IPQR variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consequences (IPQR)</td>
<td>&lt;0.001</td>
<td>0.82</td>
<td>0.75-0.90</td>
<td>0.22</td>
</tr>
<tr>
<td>Treatment Control (IPQR)</td>
<td>0.003</td>
<td>1.25</td>
<td>1.08-1.44</td>
<td>0.10</td>
</tr>
<tr>
<td>Emotional Representations (IPQR)</td>
<td>0.014</td>
<td>0.91</td>
<td>0.84-0.98</td>
<td>0.10</td>
</tr>
<tr>
<td>2) Model based on PCS/depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression (AIMS2)</td>
<td>&lt;0.001</td>
<td>0.80</td>
<td>0.71-0.91</td>
<td>0.16</td>
</tr>
<tr>
<td>Pain Catastrophizing (PCS)</td>
<td>0.001</td>
<td>0.95</td>
<td>0.92-0.98</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*Multivariable logistic regression analysis adjusted for baseline pain, diagnosis(RA/OA), and whether patients have undergone previous injection.
### Table 5: Characteristics of responders and non-responders at three and nine weeks; primary osteoarthritis patients

<table>
<thead>
<tr>
<th>Baseline Factor</th>
<th>Non-responder</th>
<th>Responder</th>
<th>Mean difference/(SE)</th>
<th>P</th>
<th>Non-responder</th>
<th>Responder</th>
<th>Mean difference/(SE)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timeline (IPQR)</td>
<td>24.54</td>
<td>23.06</td>
<td>1.48(0.87)</td>
<td>0.094</td>
<td>23.82</td>
<td>22.87</td>
<td>0.94(0.93)</td>
<td>0.324</td>
</tr>
<tr>
<td>TimeCyclical (IPQR)</td>
<td>13.98</td>
<td>13.79</td>
<td>0.18(0.76)</td>
<td>0.812</td>
<td>13.96</td>
<td>13.91</td>
<td>0.05(0.76)</td>
<td>0.944</td>
</tr>
<tr>
<td>Consequences (IPQR)</td>
<td>21.8</td>
<td>19.1</td>
<td>2.68(0.99)</td>
<td><strong>0.008</strong></td>
<td>21.91</td>
<td>17.60</td>
<td>4.31(0.94)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Personal Control (IPQR)</td>
<td>19.78</td>
<td>21.30</td>
<td>-1.52(0.70)</td>
<td><strong>0.031</strong></td>
<td>19.98</td>
<td>21.90</td>
<td>-1.93(0.67)</td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td>Treatment Control (IPQR)</td>
<td>17.36</td>
<td>18.90</td>
<td>-1.54(0.55)</td>
<td><strong>0.006</strong></td>
<td>17.64</td>
<td>19.40</td>
<td>-1.75(0.54)</td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>Coherence (IPQR)</td>
<td>17.45</td>
<td>18.00</td>
<td>-0.54(0.83)</td>
<td>0.517</td>
<td>17.21</td>
<td>18.10</td>
<td>-0.89(0.86)</td>
<td>0.307</td>
</tr>
<tr>
<td>Emotional representations (IPQR)</td>
<td>17.38</td>
<td>16.93</td>
<td>0.45(1.06)</td>
<td>0.673</td>
<td>18.18</td>
<td>15.73</td>
<td>2.45(1.02)</td>
<td><strong>0.018</strong></td>
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<tr>
<td><strong>Week 9</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain Catastrophizing (PCS)</td>
<td>21.35</td>
<td>13.89</td>
<td>7.46(2.82)</td>
<td><strong>0.010</strong></td>
<td>20.74</td>
<td>11.16</td>
<td>9.58(2.76)</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Depression (AIMS2)</td>
<td>12.02</td>
<td>9.98</td>
<td>2.04(0.74)</td>
<td><strong>0.007</strong></td>
<td>12.24</td>
<td>9.19</td>
<td>3.05(0.72)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
</tbody>
</table>
Table 6: Predictors of response at three weeks; logistic regression for primary osteoarthritis subset

<table>
<thead>
<tr>
<th></th>
<th>Univariable analysis</th>
<th>Multivariable analysis, adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P value</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>Consequences (IPQR)</td>
<td>&lt;0.001</td>
<td>0.81</td>
</tr>
<tr>
<td>Treatment Control (IPQR)</td>
<td>0.004</td>
<td>1.30</td>
</tr>
<tr>
<td>Personal Control (IPQR)</td>
<td>0.035</td>
<td>1.14</td>
</tr>
<tr>
<td>Depression (AIMS2)</td>
<td>0.010</td>
<td>0.86</td>
</tr>
<tr>
<td>Pain Catastrophizing (PCS)</td>
<td>0.012</td>
<td>0.96</td>
</tr>
</tbody>
</table>

* Multivariable logistic regression analysis adjusted for baseline pain, gender, and whether patients have undergone previous injection
Table 7: Predictors of response at nine weeks; logistic regression for primary osteoarthritis subset.

<table>
<thead>
<tr>
<th>Multivariable analysis, adjusted*</th>
<th>Univariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P value</td>
</tr>
<tr>
<td>1) Model based on IPQR variables</td>
<td></td>
</tr>
<tr>
<td>Consequences (IPQR)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment Control (IPQR)</td>
<td>0.004</td>
</tr>
<tr>
<td>Personal Control (IPQR)</td>
<td>0.008</td>
</tr>
<tr>
<td>Emotional Representations (IPQR)</td>
<td>0.022</td>
</tr>
<tr>
<td>2) Model based on PCS/depression</td>
<td></td>
</tr>
<tr>
<td>Depression (AIMS2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pain Catastrophizing (PCS)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Multivariable logistic regression analysis adjusted for baseline pain, gender, and whether patients have undergone previous injection.
Chapter 7.0  Discussion

7.1 Outline
This chapter summarises the main findings of the study, and how these findings add to the literature in the field. The strengths and limitations of the data are considered and also the clinical & research implications of the findings. Further research is outlined.

7.2 Main findings
The principal findings of this study were that patient psychological characteristics predicted short- to medium-term outcome of pain relief following intra-articular corticosteroid injection in patients with symptomatic knee osteoarthritis. By contrast, structural factors including accuracy of injection, OA-type (i.e. primary or secondary OA), radiographic severity or sonographic features of inflammation did not show any association with outcome, at least in the sample studied. Among the psychological factors studied illness perceptions and depression were the strongest predictors of outcome. In univariate analysis several domains of the IPQR emerged as associated with response including consequences, treatment control, personal control and emotional representations. In adjusted multiple regression models, higher treatment control score was an independent predictor of response at three weeks, with lower score for consequences close to reaching independent significance. At nine weeks, both higher treatment control and lower consequences were independent predictors of response to treatment and the proportion of variance explained by the model (30%) was higher than at three weeks (17%).

Higher depression and pain catastrophizing were found to be associated with a lower likelihood of response to treatment at both three and nine weeks in univariate analysis. A multivariate model containing both these variables was significantly associated with outcome at both time points; however, neither variable was an independent predictor of response at three weeks and only depression was independently linked with non-response at nine weeks. The proportion of variance explained was lower than a model based on the IPQR variables at both nine weeks
(20%) and three weeks (11%). Other factors linked with outcome (non-response) included baseline pain severity and also previous treatment by injection, with those who had had a prior injection being less likely to respond than those who had not. Neither of these factors, however, remained significant in a multiple regression analysis.

7.3 Comparison with published literature

In this section the results relating to prediction of response are compared with the published literature. Four areas are considered including i) illness perception, ii) depression & pain catastrophizing, iii) accuracy of injection and iv) structural predictors (including radiographic grade and ultrasound appearances).

7.3.1 Illness Perceptions

To date no peer-reviewed published data were found concerning the impact of illness perception on outcome following steroid injection therapy in symptomatic knee OA. According to the Common Sense Model of Leventhal (218), favourable patterns of illness perceptions, characterised by higher scores for control perceptions and lower scores for timeline and consequences will be associated with positive physical and psychological adaptation to illness. The associations between illness perceptions and outcome post IACI found in this thesis support this model.

By contrast with IACI, there are some reports looking at illness perceptions and outcome in OA in the setting of knee arthroplasty and these are consistent also with a positive association between IPs and outcome. In the analysis presented in this thesis, higher treatment control perceptions predicted a higher rate of response to (IACI) treatment. In a study of patients undergoing arthroplasty for OA, a similar relationship between higher control perceptions and better function was reported at 9 months (215), while in another higher treatment control scores predicted better outcomes at one year after hip arthroplasty (though not knee arthroplasty) (216). By contrast, data from a couple of studies reported no association between control perceptions and outcome assessed by either level of pain or knee function (187;217).
In the analysis presented in chapter six, higher consequences were found to be associated with poorer response to IACI. One previous study (187) found that higher IPQR consequences contributed to worse Oxford knee score at six weeks but not one year post TKR. Two found no relationship between consequences and outcome of arthroplasty (215;216) although in one of these, higher scores for the related domain ‘concerns’ predicted a poorer outcome in terms of American Knee Society score post TKR (216).

In the analysis presented in chapter six, no significant relationship was observed between IPQR timeline (ie higher scores denoting perceptions of more chronic illness) and outcome, although in univariate analysis there was a trend towards perceptions of a more chronic timeline being associated with non-response at three weeks. Two previous studies (216;217) found perceptions of less chronic illness to be associated with favourable outcome following arthroplasty. This may reflect an attitude some patients express that arthroplasty constitutes a ‘cure’ for arthritis, which those with stronger timeline beliefs do not share, and one which may be less relevant in the case of IACI.

In summary, previous studies of TKR have found individual IPQR domains to be inconsistently associated with treatment outcome, although reported relationships are in the direction predicted by the CSM. Individual differences in study findings may be explained by differences in methodology and may be less important than the overall pattern in which certain profiles of illness perceptions are linked to outcomes.

7.3.2 Depression and pain catastrophizing

In this study both pain catastrophizing and depression scores were lower in responders at each time point but only depression emerged as an independent negative predictor of WOMAC response at nine weeks and neither was independently significant at three weeks.

Only one previous study has looked at the impact of adverse psychological factors on outcome following IACI in knee OA. In this study no association was found between total hospital anxiety and depression score and outcome (157). However, the sample
size was relatively small (n=59), with limited power to detect an association and used a measure of distress (total HADS), rather than of depression.

The relationship between pain catastrophizing and depression and indeed the exact nature and operation of pain catastrophizing remains controversial (116;253). It has not been explored in studies of IACI. Several studies have examined catastrophizing and depression in relation to the outcomes of arthroplasty, but caution must again be exercised in making generalisations.

Edwards et al, observed an association between both depression, assessed by the Center for Epidemiological Studies Depression Scale, and catastrophizing with smaller changes in knee pain up to one year following knee arthroplasty, though only depression was significant in multiple regression(190).

By contrast, higher pain catastrophizing has been found to predict adverse outcome in several knee arthroplasty studies. Two studies by Sullivan (189;194) and a third by Riddle (188), examined the effects of depression, assessed using Personal Health Questionnaire 9 (PHQ9), and catastrophizing, using the PCS, on WOMAC pain score post knee replacement. In all three studies, higher pain catastrophizing remained an independent predictor of higher pain in the presence of depression, whereas depression did not at six weeks (189), six months (188) or one year (194) post arthroplasty. It is possible that methodological factors may in part explain some of the discrepancy in findings, with different instruments used to measure both depression and catastrophizing in the different studies.

7.3.3. Accuracy of injection and outcome

As shown in chapter five, in subjects who took part in the current study 70% of injections which were judged (by sonographic assessment) to be accurately sited in the intra-articular space resulted neither in a superior rate of response, nor a superior reduction in pain score than those injections judged to have failed to reach the intra-articular space. Sonographic assessment of accuracy was shown to be reliable. This constitutes the largest study to date to examine the effect of accuracy of steroid
placement on outcome in OA.

There are few comparative data. The data, though, are consistent with a small study undertaken by Jones et al who looked at the effect of accuracy of injection in various joints (including the knee and shoulder) in a mixed population including patients with rheumatoid arthritis and osteoarthritis (225). In this study accuracy was not linked with outcome as assessed using the Ritchie articular index (a measure of synovitis). The data were also consistent with results of a randomised, blinded study of 38 subjects with symptomatic knee OA (161). No difference in clinical outcome was observed between those randomised to deliberate extra-articular placement of steroid adjacent to tender points on the patellar margin compared to those with placement that was administered to be (but not verified as) intra-articular.

Ultrasound can improve the rate of successful fluid aspiration from joints (254) and there is evidence that ultrasound guidance can result in both more accurate injection and greater improvements in symptoms following injections than those given without imaging guidance (255-257) The assumption, however, that improvements were the result of greater accuracy(257), rather than a placebo effect relating to the experience of receiving an ultrasound- (rather than clinically) guided injection, remains unproven since the studies included no control for the use of US as a potential source of confounding. By contrast, a study employing sham and real ultrasound that compared the effects of injections given to various joints with and without guidance in inflammatory arthritis and assessed accuracy by the use of co-injected contrast showed superiority of ultrasound in accuracy of injection but not in pain reduction(227)

According to the hierarchy suggested by Zhang (201), in which invasive treatments have a larger placebo effect size than non-invasive treatments and treatment courses requiring multiple injections a greater effect size than single ones, ultrasound guided injections might be expected to be linked with a larger placebo effect than a standard injection.

7.3.4 Structural disease parameters as predictors

Both the systematic review contained in this thesis and a second published at the same
time revealed limited and contested evidence linking structural parameters with response to IACI (160;258). This study found no significant link between radiographic grade or sonographic evidence of effusion or synovial hypertrophy and response to injection at 3 or 9 weeks, although it is important to acknowledge that, in the absence of a prospective power calculation made with respect to these factors, it is not possible to exclude that failure to detect differences might have been the result of insufficient power. However, the data in relation to effusion and ultrasound-detected synovial hypertrophy is consistent with most (58;157;158;259), though not all (153;154;159) previous studies. In one RCT the presence of effusion detected clinically was linked with a greater reduction in pain at 1 week, though not 3 weeks (154). Because of the time assessments in the study reported in this thesis it is possible that an early effect may have been missed, although the clinical relevance of this observation is debatable.

In relation to disease severity as determined by radiographic grade the data are consistent also with most previous studies (150;154;156). A couple of studies have suggested that radiographically more severe disease is linked with poorer outcome (153;260). In one of these, Smith (260), examining 38 subjects with knee OA, found a lower rate of OARSI response at four weeks in those with more severe radiographic disease. However all patients in that study received arthroscopic lavage as well as IACI at baseline, making these findings difficult to generalise to other populations. Arden et al (153) found that patients with more severe radiographic disease (Kellgren Lawrence grades 3-4 disease) showed no residual benefit of IACI at six months post injection whereas symptom scores of those with milder radiographic disease (KL grade 1 or 0) had not returned to baseline, implying some residual benefit. This observation must also be interpreted with caution since no benefit of steroid over placebo has been demonstrated at six months post injection in placebo controlled trials.

Two non-structural, patient characteristics that were found to be linked to responder status in our cohort were whether or not subjects had received previous injection treatment and baseline pain; subjects with higher baseline pain and those who had received previous injections were less likely to respond to treatment. These factors were not significant in multiple regression. Baseline pain did not predict response to IACI in most previous studies (153-155), and one study suggested greater pain reduction following IACI in patients with greater baseline pain (58). Previous
experience of injection has not been examined previously as a predictor of response and will be discussed further in section 9.5.3

7.4 Strengths and Limitations

The strengths of the study include its observational nature that reflects routine practice of IACI in knee OA. Furthermore it was larger than previous studies and used US imaging to characterise the knee joint and accuracy of injection in a reliable fashion. Ultrasound assessments were undertaken by a single operator and triplicate, continuous measurements used at several sites rather than single dichotomous measures as used in previous studies. The observational design removed possible patient uncertainty about outcome that might have accompanied a placebo controlled study, as well as maximising useable data from the sample. A further strength was the use of validated, standard instruments to measure key characteristics including pain as well as the psychological characteristics studied in knee OA.

There are a number of limitations which need to be considered in interpreting the data. This was an observational study and all subjects received the intervention. It is possible that some of the response may simply be due to change in the natural history of the disease (i.e. regression to the mean) rather than a treatment effect, particularly in those with higher pain scores (although univariate data suggested an association between lower, rather than higher, pain scores and response). All of the subjects who took part were aware that they were involved in a study and also that they were receiving active therapy and both factors may therefore have influenced their response, although the latter reflects a normal treatment environment better than an RCT. The patients were all recruited from secondary care and may therefore have represented a particularly symptomatic or treatment-refractory cohort. The majority had received intra-articular steroid therapy before, which may have led to particular expectations and ideally a naive cohort would have been preferable. Conversely, this did allow confirmation that previous injection was associated with a lower rate of response to therapy. Concomitant treatment (e.g. NSAID/ opioid use) was not restricted and was not adjusted for in the analysis.
The assessor (and PhD candidate) was, inevitably aware of the hypothesis of the study, questionnaire data and radiographic and sonographic data at some stage during the course of study. Importantly, the hypothesis and radiographic and sonographic findings were not shared with the study subjects and psychological questionnaire scores were not tallied prior to patient reporting of response in order to reduce the risk of bias. Nevertheless, it could be argued that a small risk of bias remained.

A Limitation that has been acknowledged in previous sections was the uncertainty as to whether failure to detect association between response status and targeted somatic factors was the result of a lack of power. To this end post hoc power calculations were performed, looking at power to detect differences in rate of response in the sample at nine weeks according to arthrogram status, hsCRP value and ultrasound effusion grade. Each calculation assumed 80% power and alpha of 0.05 and assumed no changes in the proportion of responders to non-responders in a larger sample and no changes in SD. In the case of accuracy, it was found that a sample of 796 would be required for the observed differences to reach significance (bearing in mind that in view of direction of the difference observed, this would demonstrate that inaccurate injections were superior). Alternatively, to demonstrate superiority of accurate injection in the sample size available, a response rate of 14% would have been required in the inaccurate group as compared with the 40% rate observed in the accurate group. With respect to effusion depth, the sample had sufficient power to detect a difference of 1.25mm between groups, which is over twice that which was observed. In the case of hsCRP, it was calculated that a sample of 370 would be necessary for the observed difference in hsCRP between the groups to be significant. Overall these calculations suggest that, at minimum, a doubling in sample size would have been required for observed differences in somatic factors to be significant. This realistically places such an investigation beyond the scope of a single-centre project but arguably also questions the clinical significance of the small differences observed.
7.5 Inclusion of secondary OA

In the study participants with OA secondary to RA were included. This was primarily for pragmatic reasons to increase recruitment into the study. To avoid inclusion of patients with active inflammatory disease we defined OA in those with RA as mechanical symptoms, radiographic changes signifying OA and clinically quiescent RA. Some of these participants with RA may in fact though have had primary OA in the context of inflammatory joint disease; this is suggested by the fact that just over one in five of those with RA reported symptoms in the index joint prior to the onset of RA.

A concern, however, with inclusion of these patients is that they may have had subclinical inflammation related to their RA and that this may have impacted on their response. HsCRP was slightly higher among those with secondary OA than those with primary OA; also there was no significant difference in mean effusion or synovial thickness measurements between those with and without rheumatoid arthritis, suggesting that if there was any subclinical inflammation this was not manifest through any structural change at the index joint.

A key question however is whether or not subjects with RA behaved differently than those without in respect of outcome following IACI and also factors predicting outcome, particularly operation of psychological factors that are at the centre of the prediction models generated. In relation to outcome there did not appear to be any difference in response rate among those with and without RA. Also there was no significant effect of disease on outcome in any of the models tested. Furthermore regression models performed using the primary OA subgroup if anything suggested a higher $R^2$ than the results for the whole sample. The reason for this is unclear; although participants with RA were instructed to consider only their mechanical knee symptoms when completing the IPQR, it is not possible to exclude an effect of their RA on their overall illness perception scores or their subsequent operation, which may have impacted on their ability to predict change following a targeted knee therapy.

7.6 Use of Ultrasound

7.6.1 Accuracy
In this study, accuracy of injection was assessed using the air arthrosonogram (AAS) technique. Classification of positive AAS was dependent on demonstrating mobile air within an intra-articular space post injection. This technique was originally described as a method of verifying intra-articular placement of injections placed under direct ultrasound guidance (229). Even in joints with no discernible effusion, AAS could be demonstrated at least briefly in the vast majority of cases. Koski evaluated the reliability of this technique in 133 consecutive injections to joints and tendon sheaths (248). Inter-observer agreement between three raters seen in this study was good (84.2-88.7%) although the mean kappa value of 0.595 was lower than observed in this thesis. This may have reflected the lack of acquisition of images during injection, the varied small structures injected, the smaller volume of air (0.1-1ml) or the inclusion of an ‘uncertain’ category as well as ‘accurate’ and ‘inaccurate’ in classifying arthrograms.

Good inter-observer reliability of the technique (mean kappa 0.79) was reported in this study (chapter five). However, confirmation that the technique is reliable does not equate to saying that it is valid; this is to say that this does not confirm that a positive AAS equates to a definite intra-articular injection. No absolute gold standard exists to ascertain accuracy of localisation within the joint.

Injection under direct guidance was used in the original description. However, since all injections were intended to be intra-articular, specificity of AAS was not tested. A very high rate of positive AAS in our data would have been a concern but this did not occur since the proportion of subjects classified as positive AAS was similar to the data on accuracy of unguided injection demonstrated in a recent systematic review (261).

A previous method for testing accuracy of localisation of joint injection includes injection of contrast and detection using plain radiographs. This was not done in the current study because it can result in a high rate of indeterminate results (225), which raises questions about the validity of this technique. Cunnington’s study (227) restricted the reporting radiologist to classify x-rays with contrast as positive or negative but since only one radiologist reported the films it is impossible to comment on whether the technique was reliable. In this thesis, classification of AAS was also restricted to either positive or negative, rather than allowing a third category of ‘uncertain’. This binary classification may have oversimplified the ‘real world’ situation
in some case; for instance those in which part of the injection was intra-articular and part extra-articular, caused by movement of the needle tip during injection. This study included subjects in whom part but not all of the injectate was placed intra-articularly, resulting in classification as positive AAS. In other cases injectate was placed within a synovial layer, resulting in distribution in a layer very close to the joint but no visible mobile air and classification as negative AAS. If assessed using radiographs, however, the latter might have been classified as intra-articular.

This limitation is ultimately a general example of the way in which research studies often simplify more complex situations arising in the real world and will apply equally to any system of assessing injection localisation.

7.6.2 Assessment of synovitis

In terms of assessment of knee effusion and synovitis, the use of ultrasound provides a more sensitive measure than clinical examination (37). In contrast to previous studies that have employed ultrasound (58;159;262), this investigation employed continuous rather than dichotomous measures of synovial thickness and effusion, which should provide greater sensitivity to detect a relationship between exposure and outcome, further strengthened by repeating measurements in triplicate. Intra-class correlation coefficients for these measurements of 0.96 for effusion and 0.94-0.96 for synovial hypertrophy demonstrates excellent reliability of the technique, with similar figures for inter-observer variability reported in an earlier publication that informed this study protocol (246). Although the dichotomous measure of outcome used might have reduced the sensitivity to detect effects, post-hoc use of linear regression using absolute change in WOMAC pain scores did not reveal any relationship between US measurements and change in pain post injection.

No consensus currently exists as to the best method of assessing quantitatively the burden of inflammatory disease in the knee joint using ultrasound. While the method for measuring effusion used in this study allowed quantification across all regions of the suprapatellar pouch, it was confined to measuring one dimension only (depth). At least one other group has attempted to measure two dimensions (263). Assessment of synovial hypertrophy is further complicated by variation of morphology and
distribution. MRI imaging, by comparison, allows more accurate quantitative assessment of synovitis particularly with the use of contrast enhancement, however, to date there are no data exploring the correlation between synovitis assessed in this way and US assessment or indeed the impact of synovitis assessed in this way and outcome.

7.7 Prior experience of injection

Previous injection was associated with non-response in univariate analysis. Why might this be? One explanation could be a change in illness perceptions over time in these patients. It has been shown that IPs reported by OA patients change over time in a ‘negative’ direction characterised by higher scores for timeline and lower scores for control while pain intensity and disability increase (209). The cross-sectional data here are insufficient to demonstrate mediation (264) of the effect of previous injection by IPs but two observations suggest that this could be possible. Firstly, those who had received previous injections did have numerically ‘more negative’ patterns of IPs than those who had not had previous injection, which in the case of consequences approached significance (p=0.07). Secondly, previous experience of injection was associated with outcome in univariate logistic regression but not in a multiple regression model containing illness perceptions, whereas illness perceptions remained significant predictors of outcome after adjusting for previous injection.

7.8 By what mechanisms could psychosocial factors influence outcome?

As outlined in the introduction, the common sense model predicts that the effects of illness perceptions on outcomes are mediated through the selection of coping strategies. Two meta-analyses, however, provide only modest evidence for such mediation (237;265). Supposing the effects of illness perceptions on the outcome of injection observed were mediated by coping strategies, which were these coping strategies? One of the specific associations reported by Brooke and Lusher was between treatment control perceptions and active, problem focussed coping. These coping strategies are typically characterised by efforts to understand a problem fully
and devise practical solutions to achieve better control. In the case of the association between higher treatment control perceptions and greater response to treatment seen in the study, examples of problem focussed coping that could have impacted response might have included aspects such as greater use of exercise, more confident use of analgesia or complementary therapies and active pacing techniques. Therefore, the effects of a steroid injection might be increased in the group with higher treatment control perceptions by the use of other behaviours designed to reduce symptoms. This would appear plausible: an individual will only think it worthwhile undertaking such active strategies if they perceive some chance of success.

By contrast, the effects of high consequences in limiting improvements in pain seen following steroid injection might be explained by a combination of factors. The first of these might be a failure of active strategies as seen above, perhaps due to judgements by the individual that the problem could not be controlled in this manner. In the case of lower treatment control, this judgement would arise because of their low beliefs in the ability of treatment to impact their symptoms and, in the case of consequences, because of the perceived scale and threat of the condition itself. Instead these individuals (those with lower control and higher consequences) might employ other, less successful coping strategies such as catastrophizing, hoping for improvement, concentrating on emotion focussed strategies, exercise passive pacing or avoid potentially painful situations, which in turn would be likely to result in reduced exercise, physical deconditioning and less improvement following treatment.

In addition to variance explained by coping strategies, both meta-analyses demonstrated unexplained variance not mediated by coping; what Lusher describes as a “direct” effect of illness perceptions on health outcomes. While ‘direct’ in this sense means “not mediated by coping”, this does not preclude mediation by another psychological process. However, other possible alternative explanations include more genuinely direct neurophysiological effects caused by cognitive and/or emotional processes. A detailed discussion of these potential mechanisms is beyond the scope of this thesis; however some basic principles will be explored.
Examples of psychological - neurophysiological interactions might include cognitive distortions in the context of highly negative illness perceptions or depression, with resultant effects on areas of the brain connected with the emotional processing of pain (such as the thalamus and amygdala) and modulation of endogenous opioid pathways.

Cognitive distortions characterise Beck’s cognitive triad of depression of thoughts about self, the outside world and the future (266). An individual with highly negative profiles of illness perceptions (particularly domains such as consequences, characterised by such statements as ‘my illness has major consequences on my life’) has already made a negative judgement about at least one aspect of their situation. Beck’s theory would predict that such schemata would be generalised to influence the evaluation of symptoms relating to their disease. This could explain in part the poorer improvements in pain following treatment seen by those subjects in the study with higher scores for consequences, who still considered their symptoms to be severe in every context because of these schemata, as well as the effect of depression and potentially any effects of pain catastrophizing. It is more difficult to explain the effect of the treatment control domain in this manner, since it does not provide an obvious counterpart to depression and shares less variance than consequences.

As was shown in the introduction (section 1.2.2), the medial spinothalamic tract terminates in areas of the brain associated with emotional and affective functions (64) and such areas are stimulated selectively in arthritic as opposed to experimentally induced pain (68), providing a mechanism by which cognitive appraisal and affect could influence pain directly. Neural imaging studies suggest that such effects do occur (267), in particular leading to greater activation of limbic system structures, as well as reduced activity in the periaqueductal grey, anterior cingulate cortex and prefrontal cortex. A further factor that influences pain processing in these areas is what Price described as ‘secondary pain affect’ (268). Characteristics of secondary pain affect include concerns about how pain will affect the individual’s life and implications for the future; strikingly similar to those of the IPQR domain of consequences. It is possible therefore that the subjects in the study with higher scores for consequences might experience the same kind of alterations in pain processing at a central level that Price
describes in secondary pain affect and that these could mediate the effect on perceived treatment response.

Importantly, as well as associations with emotion, many of the brain regions described in this section are thought to contribute to the operation of the endogenous opioid system, which is discussed in more detail below.

Descending pain inhibition and more specifically the endogenous opioid system appear to have a key role in mediating placebo analgesia, as demonstrated by the abolition of placebo analgesia by naloxone (269).

Placebo analgesia is known to be modulated by expectation (270), with higher expectations of analgesia resulting in greater analgesic effect. This effect is then compounded by learning, with the confirmation of expectations through focus bias (271). PET imaging studies have demonstrated endogenous opioid release on administration of placebo analgesia (272), showing that anticipation of analgesic effect itself produces analgesia. Treatment control perceptions are not identical to outcome expectations, but sufficient similarities exist to suggest that this mechanism might also lead to greater release of endogenous opioids in the patients in the study with higher treatment control illness perceptions following steroid injection and thus resulting in additional analgesia following treatment.

Conversely, negative emotional or cognitive processes may impair the functioning of this pain-inhibitory system, reducing the effectiveness of descending inhibitory signals including endogenous opioids. Recent functional MRI studies have demonstrated that, in response to anticipated pain, patients with high scores for catastrophizing (as measured by the PCS) show reduced activity of the right lateral prefrontal cortex than normal in response to anticipated experimental pain(273). This area is involved in producing descending inhibitory signals in response to anticipated pain. The implication, therefore, is that patients with higher scores for catastrophizing will be less able to reduce the intensity of anticipated pain than those with lower scores. Furthermore, in this study the level of activation of the prefrontal cortex was inversely proportional to pain sensitivity in these patients. Importantly, therefore, the
endogenous opioid system has a role in preparing the body to cope with pain and this ability can be altered by psychological processes. Dysfunction of this system in pain catastrophizing will result in higher levels of pain in a given situation. This ‘self fulfilling prophecy’, that those who expect greater pain suffer more pain, could serve to entrench the individual’s negative expectations with respect to anticipated pain even further.

These studies therefore offer a possible common mechanism for the effect of both good anticipatory outcomes to pain (such as might characterise high treatment control illness perceptions, in which analgesia is anticipated to be effective) but also negative expectations of disease symptoms, not limited to outcome expectations relating to analgesia (as explicitly demonstrated for pain catastrophizing, but which could equally apply to cognitive distortions characterising depression or high IPQR consequences).

In summary, the Common Sense Model predicts that the effects of illness perceptions on outcome will be at least partially mediated by selection of coping strategies. However, there is some evidence from other research areas to suggest that illness perceptions, depression and catastrophizing may also have more direct effects on pain processing at a central level, mediated by key brain areas associated with cognitive/emotional processing and descending modulatory pathways, including via endogenous opioids (see Figure 4).
7.9 Implications of findings

While the study lacked prospective power calculations with respect to somatic factors, which limits the ability to draw definitive conclusions, the results observed at least suggest that structural factors including radiographic severity of knee OA and sonographic ‘inflammatory’ features including effusion and synovial thickening may not impact on outcome of pain relief in symptomatic knee OA. This would suggest that clinicians should have confidence in a therapeutic trial of IACI even in patients with advanced radiographic disease and absence of apparent clinical features of inflammation including knee effusion. Since there is no evidence that accurate intra-articular placement is a pre-requisite for response, the data suggest that routine use of imaging guidance to perform injections may not be required, though further research is needed before such a strategy be more widely adopted. By contrast, psychological factors do appear to impact on outcome and it is possible that screening for these factors on initial assessment could identify patients more or less likely to
respond to treatment. Potentially these could provide the basis for a screening tool to identify those less likely to respond to treatment. Further research though would be required to confirm the findings and determine the performance characteristics of any developed tool. Some of the psychological factors identified as predictors including illness perceptions and depression are both modifiable by intervention \((219;274)\), providing a potential strategy by which treatment response might be improved. This would be most likely to be of value if it were deployed in patients at high risk of non-response, based on negative illness perceptions or depression, prior to any proposed injection.

7.10 Future research

There are a number of future research directions suggested by the research findings presented in this thesis. These are summarised below:

7.10.1 Replicate findings with respect to outcome

Further studies are required to confirm these findings. This would be best addressed with a further observational study of a homogenous cohort of patients with primary OA, ideally recruited from primary care, without experience of previous intra-articular injection.

7.10.2 Clarify longitudinal operation of illness perceptions and explore mechanism of action

The same study design could be used to explore the longitudinal operation and mediation of IPs. To do so it would need to include at least two treatments, with measurements of IPs at baseline and between the two treatments so that the relationship between longitudinal changes in illness perceptions and the outcome of treatments could be explored. Since specific instruments for measuring pain coping strategies exist, the proposed pathway of mediation of illness perceptions by coping strategies could also be examined in the same study. Other potentially important psychological relationships could also potentially be explored, such as that between
control perceptions and self efficacy, information about which could further strengthen any proposed intervention.

7.10.3 Modifying illness perceptions to modify treatment outcomes

From a practical point of view, the most important aspect of the relationship between illness perceptions and treatment outcomes is the fact that illness perceptions are modifiable. The most exciting further development from this thesis would therefore be the design and implementation of a theory-based intervention to alter illness perceptions with the intention of improving treatment responses, and potentially disease outcomes in general. This would comprise phases of designing an intervention based on theory and previous research, demonstration that it altered illness perceptions and lastly demonstration in a controlled study that changes in illness perceptions caused by the intervention would result in improved treatment outcomes relative to subjects with comparable baseline illness perceptions who had not received intervention. Various approaches to interventions to alter illness perceptions have been considered (275) and have been successfully implemented in controlled trials for other chronic diseases (219;274). Wearden suggests that these involve ‘..both cognitive and behavioural interventions..’ and ‘...the use of behavioural experiments to test and modify cognitions..’ (275). Successful interventions have contained elements of education, challenging of negative perceptions and making plans to improve future actions in relation to disease (274).

7.10.4 Illness perceptions in other treatments for OA

The data suggest the importance of IP in treatment response in OA and it is reasonable to hypothesise that illness perceptions may also influence outcome to other commonly used treatment modalities such as physiotherapy. Further studies looking at the impact of psychological factors to the response of other common therapies in OA including for example physiotherapy would strengthen a health-economic argument for putting them at the centre of theory-based patient education programmes which would be informed by the programme above.
9.10.5 Characterisation of structural change with US

In addition to important findings relating to psychological factors, several other questions have been raised by the work contained in this thesis. On a basic level, while ultrasound is more sensitive than clinical examination in detecting effusion and synovial hypertrophy, the best method measuring each feature remains unclear. For instance, the method used in this thesis of using maximal depth and synovial thickness was not equivalent to fully quantitative measurement, since it only measured one dimension, although more extensive than two large previous investigations (40;80). By contrast, other groups have measured effusion in at least two dimensions (263). Measurement of synovium is more complex still since hypertrophy is frequently highly asymmetric, and variable in morphology both between and within subjects. The relative significance of morphological patterns and their relation to symptoms and inflammatory processes is not known. A further study comparing different methods of calculating synovitis and effusion scores, correlated with symptoms and biomarkers (particularly those in synovial fluid, better representing the local inflammatory environment) could help identify optimal methods of measurement.

7.10.6 Validation of Air Arthrogram

In this study an air arthrogram was used to assess accuracy of knee injection; however, it remains uncertain how air arthrogram compares with other methods of assessment of accuracy of localisation of steroid injection including arthograms / and MRI. Further studies comparing these methods are needed to better define the potential role of air arthrogram in assessment of accurate localisation of the needle within the joint.

7.10.7 Does accuracy of localisation impact on outcome?

The data presented here suggest that localisation within the joint does not impact on outcome. A larger randomised double blind placebo-controlled trial of clinically-guided IACI with imaging-verification of placement would be able to address this question with greater certainty. If such a trial should confirm the findings of this study
presented here, it would suggest that use of methods to assure accuracy should be limited to roles of clear benefit (eg diagnostic aspiration). Furthermore a second randomised, double-placebo and double blind trials could compare the effect of clinically-guided IACI vs IM injections (eg (276)) to investigate the role of the vicinity of steroid placement for outcome in knee OA pain.

7.11 Conclusion

This first systematic investigation of the effect of psychological factors on the outcome of intra-articular corticosteroid injections in symptomatic knee osteoarthritis has shown that the consequences and treatment control domains of illness perceptions and depression predict clinically significant response. By contrast, while lack of power cannot be excluded as an explanation, neither structural factors such as radiographic severity and measures of synovial inflammation, nor accuracy of injection appeared to impact on outcome in the sample studied. This suggests that efforts into improving responses to this commonly administered treatment might be better targeted towards identifying and modifying adverse psychological factors than modifiable structural factors such as injection accuracy.
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Appendices

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- Pain catastrophizing scale
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- Patient Information sheet for study 12 YH 0457, version 4.0
- Consent form for study 12 YH 0457, version 2.0
- Baseline pro-forma for study 12 YH 0457
- Copy of research ethics application for study 11 WM 0102
- Copy of permissions letter for study 11 WM 0102
- Copy of Research ethics application for study 12 YH 0457
- Copy of permissions letter for study 12 YH 0457
ILLNESS PERCEPTION QUESTIONNAIRE (IPQ-R) FOR KNEE OSTEOARTHRITIS

YOUR VIEWS ABOUT YOUR KNEE ARTHRITIS
Listed below are a number of symptoms that you may or may not have experienced since the onset of your knee arthritis.

Please indicate by circling Yes or No, whether you have experienced any of these symptoms since the onset of your knee arthritis, and whether you believe that these symptoms are related to your knee arthritis.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes</th>
<th>No</th>
<th>I have experienced this symptom since the onset of my knee arthritis</th>
<th>This symptom is related to my knee arthritis</th>
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</thead>
<tbody>
<tr>
<td>Pain</td>
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<tr>
<td>Sore Throat</td>
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<td>Nausea</td>
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<td>Sore Eyes</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Wheezelessness</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Headaches</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Upset Stomach</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Difficulties</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of Strength</td>
<td></td>
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</tr>
</tbody>
</table>
We are interested in your own personal views of how you now see your knee arthritis. Please indicate how much you agree or disagree with the following statements about your knee arthritis by ticking the appropriate box.

<table>
<thead>
<tr>
<th>VIEWS ABOUT YOUR KNEE ARTHRITIS</th>
<th>STRONGLY DISAGREE</th>
<th>DISAGREE</th>
<th>NEITHER AGREE NOR DISAGREE</th>
<th>AGREE</th>
<th>STRONGLY AGREE</th>
</tr>
</thead>
<tbody>
<tr>
<td>IP1 My knee arthritis will last a short time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP2 My knee arthritis is likely to be permanent rather than temporary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP3 My knee arthritis will last for a long time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP4 My knee arthritis will pass quickly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP5 I expect to have this knee arthritis for the rest of my life.</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IP6 My knee arthritis is a serious condition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP7 My knee arthritis has major consequences on my life</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP8 My knee arthritis does not have much effect on my life</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP9 My knee arthritis strongly affects the way others see me</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP10 My knee arthritis has serious financial consequences</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP11 My knee arthritis causes difficulties for those who are close to me</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP12 There is a lot which I can do to control my symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP13 What I do can determine whether my knee arthritis gets better or worse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP14 The course of my knee arthritis depends on me</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP15 Nothing I do will affect my knee arthritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP16 I have the power to influence my knee arthritis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>IP17 My actions will have no effect on the outcome of my knee arthritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP18 My knee arthritis will improve in time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP19</td>
<td>There is very little that can be done to improve my knee arthritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP20</td>
<td>My treatment will be effective in curing my knee arthritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP21</td>
<td>The negative effects of my knee arthritis can be prevented (avoided) by my treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP22</td>
<td>My treatment can control my knee arthritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP23</td>
<td>There is nothing which can help my condition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP24</td>
<td>The symptoms of my knee arthritis are puzzling to me</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP25</td>
<td>My knee arthritis is a mystery to me</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP26</td>
<td>I don’t understand my knee arthritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP27</td>
<td>My knee arthritis doesn’t make any sense to me</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP28</td>
<td>I have a clear picture or understanding of my condition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP29</td>
<td>The symptoms of my knee arthritis change a great deal from day to day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP30</td>
<td>My symptoms come and go in cycles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP31</td>
<td>My knee arthritis is very unpredictable</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>IP32</td>
<td>I go through cycles in which my knee arthritis gets better and worse.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP33</td>
<td>I get depressed when I think about my knee arthritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP34</td>
<td>When I think about my knee arthritis I get upset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP35</td>
<td>My knee arthritis makes me feel angry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP36</td>
<td>My knee arthritis does not worry me</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP37</td>
<td>Having knee arthritis makes me feel anxious</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP38</td>
<td>My knee arthritis makes me feel afraid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CAUSES OF MY KNEE ARTHRITIS
We are interested in what you consider may have been the cause of your knee arthritis. As people are very different, there is no correct answer for this question. We are most interested in your own views about the factors that caused your knee arthritis rather than what others including doctors or family may have suggested to you. Below is a list of possible causes for your knee arthritis. Please indicate how much you agree or disagree that they were causes for you by ticking the appropriate box.

<table>
<thead>
<tr>
<th>POSSIBLE CAUSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 Stress or worry</td>
</tr>
<tr>
<td>C2 Hereditary - it runs in my family</td>
</tr>
<tr>
<td>C3 A Germ or virus</td>
</tr>
<tr>
<td>C4 Diet or eating habits</td>
</tr>
<tr>
<td>C5 Chance or bad luck</td>
</tr>
<tr>
<td>C6 Poor medical care in my past</td>
</tr>
<tr>
<td>C7 Pollution in the environment</td>
</tr>
<tr>
<td>C8 My own behaviour</td>
</tr>
<tr>
<td>C9 My mental attitude e.g. thinking about life negatively</td>
</tr>
<tr>
<td>C10 Family problems or worries caused my knee arthritis</td>
</tr>
<tr>
<td>C11 Overwork</td>
</tr>
<tr>
<td>C12 My emotional state e.g. feeling down, lonely, anxious, empty</td>
</tr>
<tr>
<td>C13 Ageing</td>
</tr>
<tr>
<td>C14 Alcohol</td>
</tr>
<tr>
<td>C15 Smoking</td>
</tr>
<tr>
<td>C16 Accident or injury</td>
</tr>
<tr>
<td>C17 My personality</td>
</tr>
<tr>
<td>C18 Altered immunity</td>
</tr>
</tbody>
</table>

In the table below, please list in rank-order the three most important factors that you now believe caused YOUR knee arthritis. You may use any of the items from the box above, or you may have additional ideas of your own.

The most important causes for me:-
1. __________________________________________
2. __________________________________________
3. __________________________________________
Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 – not at all  1 – to a slight degree  2 – to a moderate degree  3 – to a great degree  4 – all the time

When I’m in pain …

1. I worry all the time about whether the pain will end.
2. I feel I can’t go on.
3. It’s terrible and I think it’s never going to get any better.
4. It’s awful and I feel that it overwhelms me.
5. I feel I can’t stand it anymore.
6. I become afraid that the pain will get worse.
7. I keep thinking of other painful events.
8. I anxiously want the pain to go away.
9. I can’t seem to keep it out of my mind.
10. I keep thinking about how much it hurts.
11. I keep thinking about how badly I want the pain to stop.
12. There’s nothing I can do to reduce the intensity of the pain.
13. I wonder whether something serious may happen.

…Total
Please check (X) the most appropriate answer for each question. These questions refer to LEVEL OF TENSION.

<table>
<thead>
<tr>
<th>DURING THE PAST MONTH...</th>
<th>Always (1)</th>
<th>Very Often (2)</th>
<th>Sometimes (3)</th>
<th>Almost Never (4)</th>
<th>Never (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How often have you felt tense or high strung?</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
</tr>
<tr>
<td>2. How often have you been bothered by nervousness or your nerves?</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
</tr>
<tr>
<td>3. How often were you able to relax without difficulty?</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
</tr>
<tr>
<td>4. How often have you felt relaxed and free of tension?</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
</tr>
<tr>
<td>5. How often have you felt calm and peaceful?</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
</tr>
</tbody>
</table>

These questions refer to MOOD.

<table>
<thead>
<tr>
<th>DURING THE PAST MONTH...</th>
<th>Always (1)</th>
<th>Very Often (2)</th>
<th>Sometimes (3)</th>
<th>Almost Never (4)</th>
<th>Never (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. How often have you enjoyed the things you do?</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
</tr>
<tr>
<td>7. How often have you been in low or very low spirits?</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
</tr>
<tr>
<td>8. How often did you feel that nothing turned out the way you wanted it to?</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
</tr>
<tr>
<td>9. How often did you feel that others would be better off if you were dead?</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
</tr>
<tr>
<td>10. How often did you feel so down in the dumps that nothing would cheer you up?</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>___</td>
</tr>
</tbody>
</table>
WOMAC VA3.1 QUESTIONNAIRE

Section A

PAIN

Think about the pain you felt in your ______________ (study joint) due to your arthritis during the last 48 hours.

(Please mark your answers with an " X ".)

QUESTION: How much pain do you have?

1. Walking on a flat surface.
   No Pain | Extreme Pain

2. Going up or down stairs.
   No Pain | Extreme Pain

3. At night while in bed.
   No Pain | Extreme Pain

4. Sitting or lying.
   No Pain | Extreme Pain

5. Standing upright.
   No Pain | Extreme Pain

Study Coordinator Use Only

PAIN1
PAIN2
PAIN3
PAIN4
PAIN5

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United Kingdom - V3
PATIENT INFORMATION LEAFLET

Steroid Injections in Knee Arthritis - Observational Study

Clinical Research Unit, Dudley Group of Hospitals

version 4 (5/05/2011)

You have been invited to take part in a research study because you have arthritis of the knee and your doctor has suggested a steroid injection into your knee to reduce your pain.

Before you decide to take part in the study it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully.

What is the study about?
At the moment, doctors know very little about which patients get the best response to steroid injections. This makes it difficult to give people good advice about how much they are likely to benefit from an injection. This study will examine several possible factors and whether these are linked to a better response in patients receiving knee injections. Some of these factors are physical characteristics, such as the levels of inflammation in the knee, and the appearances of x-rays. Some relate to psychological characteristics.

How do I get in touch?
If you are interested in taking part please contact us at your earliest convenience, either by using the telephone number or reply slip on the sheet attached and we will arrange an appointment for you.
What will I have to do?

All the injections are given as they would be in normal clinical care and all contain the same active medication (steroid mixed with local anaesthetic) as would normally be used, together with the addition of 1-2ml of air to assist ultrasound examination. Air is not usually included in knee injections given in clinic but is standard in injections assisted by ultrasound.

At the first appointment, a doctor from the research team will discuss the study in more detail and answer any questions before asking you to sign a consent form indicating that you understand what to expect from taking part in the study. Next, we will ask you to complete four questionnaires that assess the severity of your symptoms, your mood, what you believe about your illness and your experience of how you react to pain. If you have Rheumatoid Arthritis then we will assess your overall disease activity by focussed examination and a question about your impression of how well your disease is controlled at the time. As part of this study, you will have 3 x-rays of your knee, 2 of these are routine but the third is required as part of the study. The radiation exposure from these X-ray is very low and will expose you to approximately the same amount that we are all exposed to from natural background radiation in one day. Radiation is known to increase the risk of developing cancer after many years. In total the X-rays in this study will add less than 1 in 3,000,000 to the individual lifetime cancer risk. This number is very small compared with the natural cancer mortality rate in the UK of 1 in 4. We also ask you to have an ultrasound scan of the knee (which involves no radiation) and to provide a blood and urine sample which will be stored and analysed. The injection will be performed immediately after this assessment. Any fluid drawn off the knee will be stored and analysed. A second very brief ultrasound examination will follow immediately. We would expect the first visit to last 60-90 minutes. As for all patients receiving knee injections, we would advise you to rest your knee for 24 hours afterwards and that you arrange for someone to bring you to the appointment and take you home afterwards.
Three weeks later we will invite you to return to the hospital to complete a single questionnaire about your symptoms and to provide a further blood and urine sample. If you have Rheumatoid Arthritis then we will perform the same additional assessment of your overall arthritis activity as at the first visit. This second visit should last for no more than half an hour. Nine weeks after receiving the injection you will receive a questionnaire by post. We ask that you complete this and return it to the hospital in the Stamped Addressed Envelope provided.

Samples of blood, urine and synovial fluid removed from the joint will be stored in our laboratory for a maximum of three years. We may wish to use them as part of a future research study, subject to approval of the local Research Ethics Committee.

**Do I receive any payments for taking part?**
We are not able to pay people to take part but can reimburse travel costs for your second visit.

**What will happen to the information from the questionnaires and tests?**
Your General Practitioner will be informed of your participation and will be sent a copy of this information sheet but all information that we collect about you will be securely stored and remain confidential.

**What are the benefits of participation?**
Apart from having a steroid injection in your knee which will, hopefully, reduce your pain, the information we gain from your participation in the study will help us learn which patients have the best response to steroid injections in the knee. This will help us advise other people in the future.

**Are there any risks involved?**
There are no additional risks above those that are normally present in patients having steroid injections. Infection in the knee can occur in about 1 in 15,000 patients having steroid injections. Occasionally local discomfort can increase for 24-
48 hours due to a local reaction to steroid. Local bleeding can occur but is very rare.

**Do I have to sign anything?**
If you agree to participate it is necessary that you sign a consent form. This is to show that you understand what is involved and that you have read this Information Sheet. Signing this consent form does not stop you from withdrawing from the study at any time.

**Do I have to take part?**
No. It is up to you to decide whether or not to take part and you can still have an injection if you decide not to. If you would like us to arrange this for you, please contact us using the reply slip/telephone number attached.

**Will I be able to leave the study before it finishes?**
You can leave the study at any time without giving a reason and this will not affect your future clinical care in any way.

**The Research Team**
If you have any questions about the study, please feel free to contact us on one of the numbers below:

Dr George Hirsch, Research Fellow in Rheumatology, Dr Rainer Klocke, Consultant Rheumatologist
Tel 01384 456 111 (ext 1890 or 3736)

Daljit Kaur, Research Nurse
Lucy Kadiki, Research Nurse
Rheumatology Research Helpline 01384 244754
CONSENT FORM

Predictors of response to steroid injections in knee arthritis

Clinical Research Unit, Dudley Group of Hospitals

1. I confirm that I have read the patient information sheet dated 18/08/2012, (version 2) for the above study. I have the opportunity to consider the information, ask questions and have had these questions answered satisfactorily.

2. I am aware that my participation in this study is voluntary and that if I decide not to take part that this will not affect my clinical care in any way in the future. I understand that I may withdraw from the study at any time without giving a reason, without this affecting my clinical care.

3. I am aware that information collected about me that could identify me will be stored securely for up to five years and not shared with any other agency.

4. I am aware that the results of the study, which will not contain information by which I can be identified, may be published in medical journals or presented at medical conferences.

Please initial box
5. I give permission for samples of blood, urine and synovial fluid to be stored. I understand that these may be used in future research studies, subject to approval by the local Research Ethics Committee.

6. I give permission for members of the research team to contact me in the future regarding other research studies.

7. I understand that my medical records and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data and my medical records.

8. I confirm that I agree to participate in this study as described to me.

Participant Signature ................................ Name .......................... Date..................

Researcher Signature .......................... Name .......................... Date..................
Predictors of response to steroid injection in knee arthritis study Baseline Information

Trial ID number

Date

CONSENT

**Diagnosis:**
- Primary OA
- Secondary OA
- Other Knee Pain

If other knee pain, reason for failing to meet criteria

**Demographics:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Height/cm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>Weight/Kg</th>
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</thead>
<tbody>
<tr>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>BMI</th>
</tr>
</thead>
<tbody>
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<td></td>
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</tbody>
</table>

**Symptoms of OA:**

1. Knee pain in affected knee present for most days of last 3 months
   - No
   - Yes

2. Radiographic Osteophyte
   - Yes
   - No
   - <40
   - >40
   - If Yes; OA. If no go to 3
   - If No; not OA. If yes go to 4

3. Age
   - None
   - >30
   - <30
   - If none/>30 not OA, if <30 go to 5

4. Duration of Morning stiffness (mins)
   - No
   - Yes
   - <200
   - >200
   - If No; not OA. If yes OA

5. Crepitus on active movement

Where ACR/alternative criteria apply complete WOMAC pain subscale.

**Exclusion Criteria:**

- Contraindication to steroid injection
- Steroid injection within last 3/12 or oral prednisolone >7.5mg
- Uncontrolled IHD, HT, DM.
- Fibromyalgia or Widespread Pain syndrome
Questions relating to arthritis:

How long have you been suffering from frequent pain in your knee? 

If you have RA, How long have you had it? 

Do you have significant pain in your

- low back ☐
- hip ☐
- other knee ☐
- other area (record)………………………………. ☐

(Shade Worst)

If significant pain elsewhere, indicate severity pan in the worst area over last week as VAS:

No Pain ___________________________ Worst Pain Possible ___________________________
Corticosteroid Injections in Osteoarthritis Observational Study Baseline Information

Current Medication:

1. Analgesics: .......................................................... ..........................................................
   ..........................................................................................................................
   ..........................................................................................................................
   ..........................................................................................................................
   ..........................................................................................................................

2. Other: ........................................................................................................................................................................................................................................................................................................
   ........................................................................................................................................................................................................................................................................................................
   ........................................................................................................................................................................................................................................................................................................
   ........................................................................................................................................................................................................................................................................................................
   ........................................................................................................................................................................................................................................................................................................

DAS 28 (RA only):

   SJC                      VAS                  TOTAL

   TJC                      ESR

Index Joint:       Y       N

Effusion

Warmth

Tenderness

If you have had a knee injection before, please indicate how effective you felt it was overall in reducing your knee pain:

Not effective at all  As effective as I could imagine

Blood Sample

Urine Sample

Xrays
# Ultrasound Examination

**Date**

**Identification Number**

<table>
<thead>
<tr>
<th>Site</th>
<th>Synovial Fluid Thickness</th>
<th>Synovial Hypertrophy (N/H/P)</th>
<th>PDS (+/-)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
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</tr>
</tbody>
</table>

- **Midline**
- **Lateral**
- **Medial**

**Injecting Clinician**

**Approach**

**Volume SF aspirated/ml**

**Impression of effusion?**

**Arthrogram**

- Positive
- Negative
Welcome to the Integrated Research Application System

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please enter a short title for this project (maximum 70 characters)
Corticosteroids in knee osteoarthritis; an observational study

1. Is your project research?
- Yes
- No

2. Select one category from the list below:
- Clinical trial of an investigational medicinal product
- Clinical investigation or other study of a medical device
- Combined trial of an investigational medicinal product and an investigational medical device
- Other clinical trial or clinical investigation
- Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
- Study involving qualitative methods only
- Study limited to working with human tissue samples, other human biological samples and/or data (specific project only)
- Research tissue bank
- Research database

If your work does not fit any of these categories, select the option below:
- Other study

2a. Please answer the following question(s):
a) Does the study involve the use of any ionising radiation?  
- Yes
- No
b) Will you be taking new human tissue samples (or other human biological samples)?  
- Yes
- No
c) Will you be using existing human tissue samples (or other human biological samples)?  
- Yes
- No

3. In which countries of the UK will the research sites be located? (Tick all that apply)
- England
- Scotland
- Wales
- Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:
- England
- Scotland
4. Which review bodies are you applying to?

- [x] NHS/HSC Research and Development offices
- [ ] Social Care Research Ethics Committee
- [x] Research Ethics Committee
- [x] National Information Governance Board for Health and Social Care (NIGB)
- [ ] Ministry of Justice (MoJ)
- [ ] National Offender Management Service (NOMS) (Prisons & Probation)

5. Will any research sites in this study be NHS organisations?

- [ ] Yes  
- [x] No

5a. Do you want your application to be processed through the NIHR Coordinated System for gaining NHS Permission?

- [ ] Yes  
- [x] No

If yes, you must complete and submit the NIHR CSP Application Form immediately after completing this project filter, before proceeding with completing and submitting other applications.

6. Do you plan to include any participants who are children?

- [ ] Yes  
- [x] No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

- [ ] Yes  
- [x] No

Answer Yes if you plan to recruit participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the NIGB Ethics and Confidentiality Committee to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

- [ ] Yes  
- [x] No

9. Is the study, or any part of the study, being undertaken as an educational project?

- [ ] Yes  
- [x] No

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

- [ ] Yes  
- [x] No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

Date: 19/04/2011
11. Will identifiable patient data be accessed outside the clinical care team without prior consent at any stage of the project (including identification of potential participants)?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
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<tbody>
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</table>
The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familiar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
Corticosteroids in knee osteoarthritis; an observational study

Please complete these details after you have booked the REC application for review.

REC Name: South Birmingham (West Midlands)

REC Reference Number: 11/WM/0102 Submission date: 19/04/2011

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:
An observational study of somatic and psychometric factors predicting response to intra-articular corticosteroid injection in primary and secondary osteoarthritis of the knee

A2-1. Educational projects
Name and contact details of student(s):

Student 1
Title Forename/Initials Surname
Dr George Hirsch
Address Clinical Research Unit, 1st floor,
North Wing, Russells Hall Hospital
Dudley, West Midlands
Post Code DY1 2HQ
E-mail hirsch.george@dgoh.nhs.uk
Telephone 01384244807
A2-2. Who will act as Chief Investigator for this study?

- ✓ Student
- ○ Academic supervisor
- ○ Other

A3-1. Chief Investigator:

Title: Research Fellow in Rheumatology
Forename/Initials: George
Surname: Hirsch
Post: Dudley Group of Hospitals NHS foundation trust
Qualifications: BM BCh MRCP(UK)
Employer: Dudley Group of Hospitals NHS foundation trust
Work Address: Clinical Research Unit, 1st floor, North Wing, Russells Hall Hospital
Dudley
Post Code: DY1 2HQ
A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?  
This contact will receive copies of all correspondence from REC and R&D reviewers that is sent to the CI.

Title Forename/Initials Surname  
Mrs Margaret Marriott

Address  
Clinical Research Unit, 1st Floor  
North Wing, Russells Hall Hospital  
Dudley, West Midlands

Post Code  
DY01 2HQ

E-mail  
margaret.marriott@dgoh.nhs.uk

Telephone  
01384 321024

Fax  
01384 321024

A5-1. Research reference numbers. Please give any relevant references for your study:

Applicant's/organisation's own reference number, e.g. R & D (if available):
Sponsor's/protocol number:
Protocol Version:
Protocol Date:
Funder's reference number:
International Standard Randomised Controlled Trial Number (ISRCTN):
ClinicalTrials.gov Identifier (NCT number):
European Clinical Trials Database (EudraCT) number:
Project website:

Ref.Number Description | Reference Number
---|---

A5-2. Is this application linked to a previous study or another current application?  

Yes ☐ No ☐

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.
A6-1. Summary of the study. Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. This summary will be published on the website of the National Research Ethics Service following the ethical review.

We propose an observational study of patients receiving corticosteroid injections for primary and secondary osteoarthritis (OA) of the knee, with the aim of determining factors predictive of response to injection. Injections will be performed according to usual clinical practice. Patients will be assessed for a variety of physical and psychological aspects involving x-rays, ultrasound, blood and urine tests and questionnaires at the beginning of the study. Ultrasound (US) will be used to check the position of injections once performed. The variables will be examined statistically for their ability to predict pain relief at 3 and 9 weeks.

A6-2. Summary of main issues. Please summarise the main ethical and design issues arising from the study and say how you have addressed them.

An observational study raises few ethical issues. The main impositions on patients will be questionnaire load and the requirement to provide an additional serum and urine sample. They will require 3 x-ray views of the knee. It is likely that at least two of these would be acquired as part of standard care. The total additional exposure to radiation, even assuming all 3 views were required, would be unlikely to be in excess of the equivalent of two days of natural background radiation (see radiation assessment). Beyond this, their clinical care will remain as normal.

We have elected to recruit using wide eligibility criteria, in recognition of the fact that some factors which might normally be controlled for are in fact potential predictors of response. These include obesity, back pain and arthritis in the opposite knee or elsewhere. We have decided not to exclude these patients for several reasons. Firstly, it is of interest to determine whether these factors affect the patients’ perceived response to treatment. Secondly, complex exclusion criteria create difficulties for clinicians who might be involved in recruitment but have not been involved in study design. Thirdly, narrow inclusion criteria could lead to to conclusions that are difficult to transfer to a general population, since many patients with knee OA also suffer a range of comorbidities, especially back pain, obesity and arthritis elsewhere.

The anatomical approach chosen for injections will not be standardised, since selection of a particular technique may have importance for outcomes that can be demonstrated in the study, but the approach chosen in each case will be recorded. Composition of injections will be standardised and will reflect those used in normal practice. Our injection protocol will differ from normal practice in two respects. The first is that we will also include 1- within the injection mixture in order to act as contrast for a mini-arthrogram as described by Bildall. This will allow verification of the position of injections in order to verify that injections have been placed in the intra-articular space. Following the injection, the ultrasound probe will be used to determine the position of the injection. We will explain to with them, since this could potentially influence their outcome.

Use of methods of testing such as the Enzyme Linked Immunoassorbant Assay (ELISAs) we propose to use in this study requires us to determine the normal range in healthy patients. To this end we propose to recruit around 40 healthy age matched controls and measure levels of plasma high sensitivity (hs)CRP and urinary Collagen Telopeptide II (CTXII) on two occasions. We aim to recruit these controls from amongst those people accompanying patients attending our normal regular rheumatology outpatient clinic (eg spouses or other relatives). A potential ethical concern could be, were we to solicit potential participants directly, that people would feel under pressure to participate under the impression that this might influence the care given to their relative. For this reason, display of posters inviting participation will be displayed in the outpatient waiting area and volunteers recruited from among those who express interest. The actual procedures involved for these participants will be limited to a venous blood test and urine sample at baseline and a second at three weeks.

A10. What is the principal research question/objective? Please put this in language comprehensible to a lay person.

We wish to identify factors that allow clinicians to predict whether a patient is likely to have meaningful pain relief in response to corticosteroid injection to the knee at 3 and 9 weeks post injection. These factors will include x-rays, ultrasound scan appearances, blood and urine tests, psychological factors, factors related to the patient such as whether they have arthritis in other places, back pain or have high body weight. The method chosen to inject the knee will also be considered by checking the accuracy of injections with ultrasound once they have been performed.

A11. What are the secondary research questions/objectives if applicable? Please put this in language comprehensible to a lay person.

Whether response to corticosteroid injection is linked to evidence of inflammation in the joint, as measured by concentrations of Interleukin-6(IL-6), Interleukin-1(IL-1) and Tumour Necrosis Factor-α(TNF-α) in the joint fluid or fluid
white cell count (WCC).

Whether the response to corticosteroid is linked to glutamate concentrations in joint fluid.

How psychological factors compare with physical factors such as x-rays, ultrasound appearances or blood tests in predicting the reduction of pain after a corticosteroid injection.

A12. Please put this in language comprehensible to a lay person.

Injections of corticosteroid into the joint (Intra-articular corticosteroid injections, IACI) are currently widely used internationally for the treatment of pain in knee osteoarthritis (OA). Anecdotally, patients report very varied results, both in terms of reduction of pain and duration of response. Despite the use of IACI for several decades, robust clinical predictors of which individual patients respond to injections better have not been identified, beyond a suggestion in one study of better response in those with excess fluid on the knee (a.k.a. effusion). The observation that patients with effusion may respond better to injection could relate to inflammation in the joint. Since steroids are usually used to reduce inflammation, it could be suggested that this is how they might work in OA. If this is the case, then a better response in the case of patients showing signs of inflammation in the joint might be expected. It is known that psychological characteristics have significant effects on the levels of pain that individuals report and also their response to some pain relieving procedures. This aspect has not been explored in the context of IACI for knee OA.

A13. Please summarise your design and methodology. It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol.

Patients with knee osteoarthritis in whom injection is being considered will be identified by clinicians within the rheumatology and orthopaedic departments and from general practice. The study will be discussed with them and written information given including the details of the study, procedures and samples required, number of visits and length of follow-up. Permission will be sought to contact them by telephone to discuss the study further. Provided they agree to participate, a baseline visit and consent procedure will be organised immediately prior to their injection. At the baseline visit, patient demographics such as age, Body Mass Index (BMI) and smoking status and relevant medical comorbidities will be recorded. Relevant comorbidities include back pain, contralateral knee OA, hip OA, diabetes. Where significant pain outside the knee is present, patients will be asked to estimate the severity of pain using a standardised visual analogue scale, as well as its site.

The purpose of the study will be explained, procedures discussed and signed consent completed. Consent will be sought for a urine sample and venous blood sample to be taken at baseline and at 3 weeks and for these to be stored until the end of the study. Consent will also be sought for a sample of joint (synovial) fluid to be taken at the time of injection if possible, and for this to be stored until the end of the study. Consent will be sought for x-rays of the knee in 3 views, unless these have been taken within the last 6 months, and for ultrasound assessment of the knee immediately before and after the injection.

Patients will be asked to complete several questionnaires at baseline. The first of the these will be a Western Ontario and McMaster Osteoarthritis Index (WOMAC) score, with an additional measure of patient's global impression of their disease severity. The WOMAC is an internationally recognized scale for judging the impact of the severity of symptoms in arthritis in various situations. The psychological questionnaires include measures of how patients react to pain (13 questions), what they believe about their illness (38 questions) and whether they show signs of depression or anxiety (10 questions). Patients who also have Rheumatoid Arthritis will have a standard assessment of their disease activity (DAS28), which includes a brief examination of 28 joints for signs of inflammation and a single question about the level of symptoms currently caused by their arthritis.

Injections will be performed immediately following ultrasound assessment by a clinician blinded to ultrasound findings, using an injection of standard composition and including 1.5-2 ml of air, administered by whichever technique of injection they feel is appropriate. The approach used will be recorded. Removal of synovial fluid (aspiration) will routinely precede injection and, as in normal clinical practice, injecting clinicians will remove all synovial fluid they can. Where synovial fluid has been removed, 5ml will stored as per consent. Following injection ultrasound will be used to confirm whether or not the injection has accurately entered the joint by using the air as a marker. Patients will not be advised of the findings, as specified in A6-2. Patients will be advised to rest for 24 hours following the procedure.

Repeat assessments of outcomes will be performed at 3 and 9 weeks and repeat blood testing and urine testing will be undertaken at 3 weeks, as detailed in the consent. Patients will be invited to attend for a review at the hospital at 3 weeks (+/- 3 days), at which repeat blood and urine testing will be performed. Patients will be asked to complete an outcome questionnaire comprising WOMAC, patient global assessment and a single question about the frequency of medication use. Patients who have Rheumatoid Arthritis will have a further DAS28 assessment at this point. Patients unable to attend review at this point will be invited to return a questionnaire by post. All questionnaires for the final
Factors being examined as potential predictors of response will be examined by correlation with whether or not patients respond to corticosteroid injection at 3 and 9 weeks. Response is predefined as a reduction of 40% in pain score from baseline to each of these time-points.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- Design of the research
- Management of the research
- Undertaking the research
- Analysis of results
- Dissemination of findings
- None of the above

Give details of involvement, or if none please justify the absence of involvement.
Members of our patient support groups have been consulted on the information about the study given to patients and the consent forms and will advise about organizing study visits to maximise convenience to those participating in the study.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

- Primary Knee OA (as defined by ACR criteria)
- OR Patients with Rheumatoid Arthritis with secondary osteoarthritis (as defined by persistent knee pain characteristic of OA for greater than 6 weeks and radiographic changes consistent with OA)
- clinician considering intra-articular steroid injection as a form of management
- WOMAC pain subscale score above 40mm at baseline

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

- lack of informed consent to the study
- previous corticosteroid injection within the preceding 3 months (intra-articular or intra-muscular)
- Co- Existing Inflammatory Arthritis other than Rheumatoid Arthritis
- use of oral steroid >7.5mg prednisolone or equivalent
- existent diagnosis of fibromyalgia or other chronic widespread pain disorder
- Patients with contraindication to intra-articular steroid injection will also be excluded such as those with bleeding diathesis, active current infection, chronic leg ulcer, uncontrolled diabetes or uncontrolled hypertension, allergy to triamcinolone or lignocaine preparation.

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. These include seeking consent, interviews, non-clinical observations and use of questionnaires.

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

<table>
<thead>
<tr>
<th>Intervention or procedure</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent</td>
<td>1</td>
<td>0</td>
<td>15min</td>
<td>Research Fellow, Research Nurses Clinical Research Unit, RHH</td>
</tr>
<tr>
<td>Completion of outcome questionnaire (WOMAC, patient global assessment and medication frequency question)</td>
<td>3</td>
<td>0</td>
<td>10min</td>
<td>Patients. Initial questionnaire will be filled out at baseline in Clinical Trials Unit, RHH. Second and third questionnaires can be filled out by patients at their convenience at the appropriate time point and returned to the department.</td>
</tr>
<tr>
<td>completion of psychological questionnaires (IPQR, PCS and AIMS)</td>
<td>1</td>
<td>0</td>
<td>30 min</td>
<td>Patients at baseline. Clinical Trials Unit, RHH.</td>
</tr>
</tbody>
</table>

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.

Please complete the columns for each intervention/procedure as follows:
1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

<table>
<thead>
<tr>
<th>Intervention or procedure</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray of knee to be injected from 3 directions: Anterior-Posterior, lateral and 'sky-line'-unless available already and within six month of intervention. These will occur on ONE occasion only.</td>
<td>3</td>
<td>2</td>
<td>20</td>
<td>Radiology Dept, Russells Hall Hospital</td>
</tr>
<tr>
<td>Venous blood test a baseline and 3 weeks</td>
<td>2</td>
<td>0</td>
<td>5</td>
<td>Research Fellow/ Clinical Scientist, Clinical Research Unit, RHH</td>
</tr>
<tr>
<td>Ultrasound scan of the knee</td>
<td>1</td>
<td>0</td>
<td>25</td>
<td>Research Fellow/ R. Klocke Clinical Research Unit, RHH</td>
</tr>
<tr>
<td>Arthrocentesis; aspiration of fluid and injection of steroid and anaesthetic</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>Senior rheumatology staff, Clinical Trials Unit, RHH.</td>
</tr>
<tr>
<td>Ultrasound scan to confirm position of injection</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>Research Fellow/ R.Klocke Clinical Research Unit, RHH</td>
</tr>
<tr>
<td>Urine sample at baseline and 3 weeks</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>Clinical Trials Unit, RHH</td>
</tr>
<tr>
<td>DAS28 score of generalised disease activity (Rheumatoid Arthritis patients only)</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>Research Fellow/ Research Nurses Clinical Research Unit, RHH</td>
</tr>
</tbody>
</table>

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

☐ Yes  ☐ No

A21. How long do you expect each participant to be in the study in total?

9 weeks from intervention to final assessment.
A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

The main burden for patients is the completion of questionnaires at the first visit and being required to attend for a second visit which is not part of their normal care.
They will also be required to provide two blood samples and two urine samples that would not be required under normal circumstances, and potentially up to three x-rays of the affected knee, although in practice it is likely that at least two of these x-rays will already have been taken as part of their standard case. Ultrasound scan will be undertaken immediately prior to injection and a rapid confirmation of the position of injection immediately after it.
We will aim to minimise the financial burden and inconvenience to patients of a further visit by reimbursing their travel costs for the second visit.
The risk of infection posed by the injection procedure itself is no greater than that posed by standard care and is quoted to be 1/15000 injections.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

☐ Yes  ☐ No

A24. What is the potential for benefit to research participants?

The main benefit for patients is receiving an injection to reduce their symptoms. The fast-track system of referral we propose from general practice will allow them to receive this much more quickly than they would do as part of normal clinical care.
Because of additional contact at three weeks, they will also be subject to closer surveillance than normal in the case of complications occurring.
Details of objective measurement of patients' response to treatment and their x-ray findings will be reported to GPs once they have completed their final outcome questionnaire.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.

Since this intervention is given as part of usual care, further provision for repeat injections will also be made by the team normally delivering patient care, if deemed appropriate.

A26. What are the potential risks for the researchers themselves? (if any)

none

Recruitment and Informed Consent

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used? For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).

Patients will be identified by the clinicians referring patients for injection (general practitioners, rheumatologists etc). At the time of referral, the study will be discussed with them and a written Patient Information Sheet given to them.
Referrals will be accepted from rheumatology, orthopaedics and participating general practices in catchment area of the Dudley Group of Hospitals.
A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

☐ Yes  ☐ No

Please give details below:

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

☐ Yes  ☐ No

If Yes, please give details of how and where publicity will be conducted, and enclose copy of all advertising material (with version numbers and dates).

Posters inviting participation of normal controls will be displayed in rheumatology outpatients as already described.

A29. How and by whom will potential participants first be approached?

Initial approach will be made by clinicians referring patients for injection, written information given and permission sought to contact them by telephone. Telephone contact will be made by the researcher in order to discuss further details and arrange an appointment if agreed by the patient.

A30-1. Will you obtain informed consent from or on behalf of research participants?

☐ Yes  ☐ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

Consent will be taken in written form by the research fellow. Written information, in any cases where it has not been given to the patient by the referring clinician, will be sent to the patient prior to their appointment, to ensure that they have the chance to read it in full a minimum of 24 hours before consent. The full details will explained again verbally and any questions answered prior to consent being signed.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

☐ Yes  ☐ No

A31. How long will you allow potential participants to decide whether or not to take part?

Participants will have the time between the initial proposal and the time of their injection to decide on whether to participate, since their baseline appointment will take place immediately before their injection. Written information should allow them to make an informed decision prior to their baseline visit.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

☐ Yes  ☐ No  ☐ Not Known
A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? (e.g. translation, use of interpreters)

Patients will not be enrolled if unable to understand spoken English. Where unable to read written information in English, this will be explained fully to the patient in a verbal form.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

If such an eventuality should arise, patients will be contacted by telephone, although it is difficult to imagine this situation arising, given that only one procedure will occur at the beginning of the study. The intervention is given frequently in routine clinical care and has a proven safety record.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? Tick one option only.

- The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
- The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
- The participant would continue to be included in the study.
- Not applicable – informed consent will not be sought from any participants in this research.

Further details:

If you plan to retain and make further use of identifiable data/tissue following loss of capacity, you should inform participants about this when seeking their consent initially.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? (Tick as appropriate)

- Access to medical records by those outside the direct healthcare team
- Electronic transfer by magnetic or optical media, email or computer networks
- Sharing of personal data with other organisations
- Export of personal data outside the EEA
- Use of personal addresses, postcodes, faxes, emails or telephone numbers
- Publication of direct quotations from respondents
- Publication of data that might allow identification of individuals
- Use of audio/visual recording devices
- Storage of personal data on any of the following:
- Manual files including X-rays
- NHS computers
- Home or other personal computers
Further details:
Patient data relevant to the study including contact details will be stored on secure computer terminals within CRU.

Non-identifiable data (outcome assessment data etc.) will be stored on encrypted laptop computer, under identification number assigned to each patient for the study. No personal data will be stored in this manner.

A38. How will you ensure the confidentiality of personal data? Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.

Patients will be allocated a unique identification number at baseline and this used to identify their clinical data throughout the study, outside the core record of participants.

A40. Who will have access to participants’ personal data during the study? Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.

Research fellow: All consent will be sought by this clinician
Research Nurses may retrieve specific data on request in order to allow reports of x-rays and assessment of WOMAC response to be transmitted to GPs by the research fellow without breaking blinding. Although carrying out this service patients.

Storage and use of data after the end of the study

A43. How long will personal data be stored or accessed after the study has ended?

☐ Less than 3 months
☐ 3 – 6 months
☐ 6 – 12 months
☐ 12 months – 3 years
☐ Over 3 years

If longer than 12 months, please justify:
We plan to conduct a subsequent interventional study following the observational study. Part of the design of this will include identification of factors predictive of injection. Since it is possible that factors identified in the second study will not have been addressed in the observational study, it is conceivable that examination of these could be conducted on our original cohort, where permission was granted and this was plausible. This would be impossible were the identifiable data of patients in the observational study destroyed prior to the completion of the second.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

☐ Yes ☐ No

If Yes, please give details. For monetary payments, indicate how much and on what basis this has been determined. Reimburse transport costs to second appointment equivalent to parking costs or return trip by public transport.

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?
A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

☐ Yes  ☐ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants’ General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

☐ Yes  ☐ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

☐ Yes  ☐ No

It should be made clear in the participant’s information sheet if the GP/health professional will be informed.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

☐ Yes  ☐ No

Please give details, or justify if not registering the research.
The study will be registered in the ISRCTN Register according to the declaration of Helsinki.

A51. How do you intend to report and disseminate the results of the study? Tick as appropriate:

☐ Peer reviewed scientific journals
☐ Internal report
☐ Conference presentation
☐ Publication on website
☐ Other publication
☐ Submission to regulatory authorities
☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
☐ No plans to report or disseminate the results
☐ Other (please specify)

A53. Will you inform participants of the results?

☐ Yes  ☐ No

Please give details of how you will inform participants or justify if not doing so.
A lay summary of results will be made available to patients who have participated in the research and sent to them on completion of the study.
A54. How has the scientific quality of the research been assessed? Tick as appropriate:

- [ ] Independent external review
- [ ] Review within a company
- [ ] Review within a multi-centre research group
- [x] Review within the Chief Investigator’s institution or host organisation
- [x] Review within the research team
- [x] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:

Review has been conducted according to formal process within the sponsor’s organisation. No questions were raised and the questions posed were perceived to be straight-forward.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? Tick as appropriate:

- [ ] Review by independent statistician commissioned by funder or sponsor
- [ ] Other review by independent statistician
- [ ] Review by company statistician
- [ ] Review by a statistician within the Chief Investigator’s institution
- [x] Review by a statistician within the research team or multi-centre group
- [ ] Review by educational supervisor
- [ ] Other review by individual with relevant statistical expertise
- [ ] No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

Forename/Initials Surname
Mr Peter Nightingale

Department Welcome Trust Clinical Research Facility
Institution University Hospitals Birmingham
Work Address 1st Floor, Blue Zone
Queen Elizabeth Hospital
Birmingham
Post Code B15 2TH
Telephone 0121 472 1311, ext 2586
Fax
E-mail P.G.Nightingale@bham.ac.uk

Please enclose a copy of any available comments or reports from a statistician.
A57. What is the primary outcome measure for the study?
Response as defined by 40% fall in WOMAC pain subscale from baseline values at week 3.

A58. What are the secondary outcome measures? (if any)
WOMAC responder status at 9 weeks (reduction of WOMAC pain sub-scale by 40% relative to baseline).
Osteoarthritis Research Society International (OARSI) response at 3 and 9 weeks. This uses 100mm Visual Analogue Scale (VAS) measurements for pain, function (both of which can be extracted from the WOMAC scores) and patient global assessment. A response is defined as:

≥50% change in pain or function and ≥20 absolute change in the same domain
OR improvement of 2 of 3 of:
1. pain ≥20% and absolute change ≥10
2. function ≥20% and absolute change ≥10
3. patient global assessment ≥20% and absolute change ≥10

A59. What is the sample size for the research? How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.
Total UK sample size: 340
Total international sample size (including UK): 340
Total in European Economic Area:

Further details:
300 of the above sample will be composed of participants receiving injections (150 patients with primary and 150 with secondary osteoarthritis) and 40 will be the normal controls, whose involvement will be limited, as described above.

A60. How was the sample size decided upon? If a formal sample size calculation was used, indicate how this was done.

Based on requirements for sufficient patients to preserve a ratio of 10 patient events per potential predictive variable to be entered into forward stepwise regression analysis. The expected event rate for the primary outcome measure is estimated as 50%, based on Arden et al (Osteoarthritis Cart, 2008, 16: 16:733).
This sample size allows for a loss of at least 10 percent of patients from the study and allows inclusion of the full number of proposed predictors in the forward stepwise regression analysis.

A61. Will participants be allocated to groups at random?
☐ Yes  ☐ No

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

The ability of individual variables to predict the response to corticosteroid injection at 3 weeks, as defined by WOMAC response above, will be examined using univariate analysis. Factors suggested by univariate analysis to be associated with response will be entered into the forward stepwise regression analysis. Factors will not be entered into the analysis beyond the point where the ratio of events to predictive variables is greater than 10.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. Please include all grant co-applicants, protocol co-authors and other key members of the Chief Investigator’s doctoral student researchers.
Title: Forename/Initials Surname
Dr. Rainer Klocke

Post: Consultant Rheumatologist

Qualifications: MD MRCP PhD
Dudley Group of Hospitals NHS Foundation Trust
Rheumatology Department
Russells Hall Hospital
Dudley, West Midlands

Post Code: DY01 02HQ
Telephone: 01384244807
Fax: 01384244808
Mobile: 07906017093
Work Email: rainer.klocke@dgoh.nhs.uk

Title: Forename/Initials Surname
Professor George Kitas

Post: Head of Research and Development

Qualifications: MD PhD FRCP

Employer: Dudley Group of Hospitals NHS Foundation Trust

Work Address: Clinical Research Unit, 1st Floor
North Wing, Russells Hall Hospital
Dudley, West Midlands

Post Code: DY1 2HQ
Telephone: 01384244807
Fax: 01384244808

Work Email: gd.kitas@dgoh.nhs.uk

Title: Forename/Initials Surname
Mrs. Lucy Kadiki

Post: Research Nurse

Qualifications

Employer: Dudley Group of Hospitals NHS Foundation Trust

Work Address: Clinical Research Unit, 1st Floor
North Wing, Russells Hall Hospital
Dudley, West Midlands

Post Code: DY1 2HQ
Telephone: 01384244754
Fax: 01384244808
Mobile
Work Email: lucy.kadiki@dgoh.nhs.uk

Title: Forename/Initials Surname
Mrs. Daljit Kaur

Post: Research Nurse

Qualifications

Employer: Dudley Group of Hospitals NHS Foundation Trust

Work Address: Clinical Research Unit, 1st Floor
North Wing, Russells Hall Hospital
Welcome to the Integrated Research Application System

The main benefit for patients is receiving an injection to reduce their symptoms. The fast improvement in symptoms is likely due to the corticosteroid. Those patients who have OA of the hip have a further DAS28 assessment. Patients who have Rheumatoid Arthritis will have a further DAS28 assessment at this point. Patients many patients with knee OA also suffer a range of comorbidities, especially back pain, obesity and arthritis elsewhere.

Injections of corticosteroid into the joint (Intraarticular corticosteroid injections, IACI) are currently widely used for treatment of knee OA. We aim to recruit these controls from amongst those people accompanying patients on the Ward who have OA of the knee. Following the injection, the ultrasound probe will be used to determine the position of the injection. We will explain to patients the position of the injection on the skin and mark the site of the injection for future reference. We will also explain the possible side-effects of the procedure, i.e. pain at the site of injection and local swelling. The injection will be given with a 25-gauge needle under ultrasound guidance. One injection of 5 ml of methyl-prednisolone is performed to each knee. Our original cohort, where permission was granted and this was plausible. This would be impossible were the sample size too large.

Venous blood test a baseline and 3 weeks later for CRP and Chloride. The dose and risk assessment should be set out below. Unanticipated high CRP levels would warrant recall of the patient for clinical review, other review by independent statistician, Other.

Total duration:
Daily administration of methyl-prednisolone for 7 days. As detailed in section B9, unanticipated high CRP levels would warrant recall of the patient for clinical review, Other.

Do not simply reproduce or refer to the protocol. Please give any relevant references for your study:

1. Is your project research?

2. Include procedures which might be required assessments for sub...
### A64. Details of research sponsor(s)

#### -1. Sponsor

**Lead Sponsor**

- **Status:**  
  - ☐ NHS or HSC care organisation  
  - ☐ Academic  
  - ☐ Pharmaceutical industry  
  - ☐ Medical device industry  
  - ☐ Local Authority  
  - ☐ Other social care provider (including voluntary sector or private organisation)  
  - ☐ Other  

_If Other, please specify:_

**Contact person**

Name of organisation: Dudley Group of Hospitals NHS Foundation Trust  
Given name: Margaret  
Family name: Marriott  
Address: Clinical Research Unit, 1st Floor, North Wing, Russells Hall Hospital  
Town/city: Dudley, West Midlands  
Post code: DY1 2HQ  
Country: UNITED KINGDOM  
Telephone: 01384 321024  
Fax: 01384 321024  
E-mail: margaret.marriott@dgoh.nhs.uk

**Is the sponsor based outside the UK?**  
- ☐ Yes  
- ☐ No  

_Under the Research Governance Framework for Health and Social Care, a sponsor outside the UK must appoint a legal representative established in the UK. Please consult the guidance notes._

### A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?  
- ☐ Yes  
- ☐ No  

_Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6- reasons for the unfavourable opinion have been addressed in this application._

### A68. Give details of the lead NHS R&D contact for this research:

<table>
<thead>
<tr>
<th>Title</th>
<th>Forename/Initials</th>
<th>Surname</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mrs</td>
<td>Margaret</td>
<td>Marriott</td>
</tr>
</tbody>
</table>

Date: 19/04/2011
A69-1. How long do you expect the study to last in the UK?

Planned start date:  
Planned end date:  
Total duration:  
Years: 1  Months: 6  Days: 0

A70. Definition of the end of trial, and justification in the case where it is not the last visit of the last subject undergoing the trial (1)

Final follow-up visit of last subject recruited to the trial.

A71-1. Is this study?

- Single centre
- Multicentre

A71-2. Where will the research take place? (Tick as appropriate)

- England
- Scotland
- Wales
- Northern Ireland
- Other countries in European Economic Area

Total UK sites in study 1

Does this trial involve countries outside the EU?

- Yes
- No

A72. What host organisations (NHS or other) in the UK will be responsible for the research sites? Please indicate the type of organisation by ticking the box and give approximate numbers of planned research sites:

- [ ] NHS organisations in Wales 1
- [ ] HSC organisations in Northern Ireland
- [ ] GP practices in England
- [ ] GP practices in Wales
A75-1. Will a data monitoring committee (DMC) be convened?

☐ Yes  ☒ No

If Yes, please forward details of the membership of the DMC, its standard operating procedures and summary reports of interim analyses to the Research Ethics Committee which gives a favourable opinion of the study (or to GTAC if applicable).

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

We do not anticipate that this would be likely, since therapeutic procedures are as per usual practice. One criterion would be an unanticipated high rate of infection (three or more infections).

A76. Insurance/ indemnity to meet potential legal liabilities

Note: in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? Please tick box(es) as applicable.

Note: Where a NHS organisation has agreed to act as sponsor or co-
Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

☑ NHS indemnity scheme will apply (NHS sponsors only)
☐ Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? Please tick box(es) as applicable.

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

☑ NHS indemnity scheme will apply (protocol authors with NHS contracts only)
☐ Other insurance or indemnity arrangements will apply (give details below)
A76-3. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
☐ Research includes non-NHS sites (give details of insurance/indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

☐ Yes ☐ No

Please enclose a copy of relevant documents.

PART B: Section 3 – Exposure to ionising radiation

Complete sub-sections A and/or B as applicable with input from relevant experts. It is advisable to discuss the proposed research at an early stage with (a) a Medical Physics Expert and (b) a Clinical Radiation Expert, who will carry out the required assessments for sub-sections C and D. The lead MPE can also facilitate the completion of sub-sections A and/or B if necessary.

1. Does the study involve exposure to radioactive materials?

☐ Yes ☐ No

2. Does the study involve other diagnostic or therapeutic ionising radiation?

☐ Yes ☐ No

A. Radioactive materials

Details of radioactive materials

B. Other ionising radiation

B1. Details of other ionising radiation

Give details by completing the table below:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No of procedures</th>
<th>Estimated procedure dose (use national Diagnostic Reference Levels where available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP, lateral and sky-line plain x-rays of the knee</td>
<td>3 X-rays on one</td>
<td>Total effective dose to standard subject</td>
</tr>
</tbody>
</table>
C. Dose and risk assessment

C1. What is the total research protocol dose from the exposures in A1 and/or B1, and what component of this is the additional dose over and above standard practice? What are the risks associated with these two doses (total and additional)?

The dose and risk assessment should be set out below. This should be prepared by a Medical Physics Expert (MPE) who is a registered health care professional and has expertise relevant to the planned exposures. Where the study involves different types of exposure (for example, both radioactive materials and other ionising radiation, or more than one imaging method), advice may need to be sought from other MPEs with relevant expertise. The lead MPE should produce a combined assessment for the ethics committee, giving the names of any other MPEs who have contributed to the assessment. Further guidance is available by clicking on the information button or in the document “Approval of research involving ionising radiation”, available here: http://www.nres.npsa.nhs.uk/applicants/guidance/

For a standard patient the total effective dose from all 3 views is estimated as 0.006mSv, of which 0.002 mSv is from the third view not routinely performed.

0.006 mSv corresponds to approximately 1 day of background radiation in the uk. The excess risk of fatal cancer induction from a dose of 0.006mSv is estimated as 1 in 3 million to a healthy adult aged 40 in the uk, compared with a natural incidence of around 1 in 4. The excess risk of fatal cancer from the 0.02mSv for the extra view is around 1 in 10 million.

The medical and dental guidance notes denote radiation risks in research of this level as class I or trivial requiring minor societal benefit for justification.

A dose constraint may need to be set at locally for each participating site based on the maximum excess radiation compared with their standard practice.

Special attention must be paid to pregnant/potentially pregnant women or those who are breast feeding, or other potentially vulnerable groups.

C2. Declaration by lead Medical Physics Expert

I am satisfied that the information in sub-sections A and/or B and the assessment in sub-section C provide a reasonable estimate of the ionising radiation exposure planned in this research and the associated risks.

This section was signed electronically by Mr Mark Rawson on 18/02/2011 11:04.

Job Title/Post: Consultant Physicist
Organisation: Royal Wolverhampton Hospitals NHS Trust
Email: Mark.rawson@nhs.net

C3. Details of person acting as lead Medical Physics Expert

<table>
<thead>
<tr>
<th>Title</th>
<th>Forename/Initials</th>
<th>Surname</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr</td>
<td>Mark</td>
<td>Rawson</td>
</tr>
</tbody>
</table>

Post: Consultant Physicist

Details of professional registration: CS01873

Organisation: Royal Wolverhampton Hospitals NHS Trust

Address: Dept of Medical Physics
The Deanesly Centre, New Cross Hosp
D. Clinical assessment

This sub-section should be completed by a Clinical Radiation Expert (CRE) who is a registered health professional with clinical expertise relevant to the planned exposures. The assessment should cover potential exposure at all research sites, taking account of possible variation in normal clinical practice. Where the study involves different types of exposure (for example, both radiotherapy and other ionising radiation), advice may need to be sought from other CREs with relevant expertise. The lead CRE should produce a combined assessment for the ethics committee, giving the names of any other CREs who have contributed to the assessment. The guidance notes give advice to Chief Investigators on who can act as lead Clinical Radiation Expert (CRE) and advice for the CRE on the assessment of exposures having regard to IRMER.

Special attention must be paid to pregnant/potentially pregnant women or those who are breast feeding, or other potentially vulnerable groups.

D1. Will the exposure exceed the exposure that might be received as part of normal care at any proposed research site?

☐ Yes  ☐ No

D2. Assessment of additional exposure

Explain how the planned exposure compares with normal practice and assess whether it is appropriate, using language comprehensible to a lay person. Consideration should be given to the specific objectives of the exposure, the characteristics of participants, the potential diagnostic or therapeutic benefits to the participant, the potential benefits to society, the risk to the participant and the availability of alternative techniques involving less, or no, ionising radiation.

If pregnant or breast-feeding mothers are to be studied give reasons and details of special radiation protection measures to be taken.

Occasional third view is requested by orthopaedic surgeons, which is not routinely performed in OA assessment. This is justified in the context of this study, as has been explained in previous sections.

D3. Declaration by lead Clinical Radiation Expert

I am satisfied that the exposure to ionising radiation planned in this research study (as defined in A1 and/or B1) is reasonable and that the risks are adequately described in the participant information sheet for the study.

Signature:…………………………. Date: 17/03/2011

D4. Details of lead Clinical Radiation Expert

Title Forename/Initials Surname
Dr R Shave

Post Details of professional registration
consultant radiologist
Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project is provided by Dudley Group of Hospitals NHS Foundation Trust.

Date: 17/03/2011 (dd/mm/yyyy)

Reference: 11/WM/0102

NHS REC Form

Organisation: Dudley Group of Hospitals NHS Foundation Trust
Address: Russells Hall Hospital
Dudley, W.Midlands
Post Code: DY1 2HQ
Telephone: -
Fax: -
Mobile: -
Email: rm.shave@dgoh.nhs.uk

Declarations

Employers responsible for radiation facilities at research sites must have written procedures to meet the requirements of the Ionising Radiation (Medical Exposure) Regulations 2000 (IRMER). R & D offices for NHS sites will seek confirmation from local radiation experts that local IRMER authorisation procedures have been followed. Where the local Medical Physics Expert or IRMER Practitioner disagrees with the assessments made in this Section and/or the care organisation is unable to adhere to the protocol, this should be discussed with the Chief Investigator and the lead experts for the study. Any necessary variation in the protocol or participant information sheet at particular sites should be notified to the main REC as a substantial amendment and an ethical opinion sought.
Part B: Section 5 – Use of newly obtained human tissue (or other human biological materials) for research purposes

1. What types of human tissue or other biological material will be included in the study?
   Synovial fluid aspirated at the time of joint aspiration.
   Venous blood samples.
   Urine samples.

2. Who will collect the samples?
   Initial blood and urine samples will be collected by the Research Fellow.
   Week 3 samples will be collected by the Biomedical Scientist as part of the week 3 review.
   Synovial fluid samples will be collected by the research fellow at the time of aspiration. Aspiration itself will be undertaken by a senior member of the rheumatology team.

3. Who will the samples be removed from?
   - Living donors
   - The deceased

4. Will informed consent be obtained from living donors for use of the samples? Please tick as appropriate
   In this research?
   - Yes
   - No
   In future research?
   - Yes
   - No
   - Not applicable

5. Will any tissues or cells be used for human application or to carry out testing for human application in this research?
   - Yes
   - No

8. Will the samples be stored? [Tick as appropriate]
   In fully anonymised form? (link to donor broken)
   - Yes
   - No
   In linked anonymised form? (linked to stored tissue but donor not identifiable to researchers)
   - Yes
   - No
   If Yes, say who will have access to the code and personal information about the donor.
   Personal information will be stored on an encrypted database. The research fellow will have access to this data but this will not be utilised until completion of the study.
   Each patient will be identified universally in the study by a unique identification number. This will apply to all biological samples, radiology and patient reported outcomes.

   In a form in which the donor could be identifiable to researchers?
   - Yes
   - No

9. What types of test or analysis will be carried out on the samples?
   1. Serum high sensitivity CRP testing by ELISA
2. Serum IL-6 (in Rheumatoid arthritis patients only) This indicates the level of systemic inflammation.
3. Urine CTXII testing by ELISA This relates to the level of cartilage degradation occurring.
4. Synovial Fluid IL-6 testing by ELISA. This relates to the level of inflammation within the joint.
5. Synovial fluid White cell count This relates to the level of inflammation within the joint.
6. Synovial fluid TNF alpha This relates to the level of inflammation within the joint.
7. Synovial fluid glutamate High levels of glutamate have been observed in patients with osteoarthritis. It is postulated that higher levels may relate to increased pain levels.

No ethical issues are anticipated in connection with these tests, although very high CRP levels would warrant further investigation as a sign of pathology other than osteoarthritis but would not necessarily constitute reasons for withdrawal from the trial, since no further experimental procedure would be planned.

10. Will the research involve the analysis or use of human DNA in the samples?

☐ Yes  ☐ No

11. Is it possible that the research could produce findings of clinical significance for donors or their relatives?

☐ Yes  ☐ No

12. If so, will arrangements be made to notify the individuals concerned?

☐ Yes  ☐ No  ☐ Not applicable

If No, please justify. If Yes, say what arrangements will be made and give details of the support or counselling service.

As detailed in section B9, unanticipated high CRP levels would warrant recall of the patient for clinical review, principally to ensure no evidence of infection is present. Under these circumstances, the patient will be contacted by telephone and reviewed on the Clinical Research Unit within 24 hours as necessary.

No results would have immediate prognostic or predictive significance for either patients or relatives beyond this possibility.

13. Give details of where the samples will be stored, who will have access and the custodial arrangements.

Samples will be stored within the laboratory facilities at the Clinical Research Unit.
This area is under the supervision of Jackie Smith, Senior Biomedical Scientist. Access will be restricted to Jackie Smith and Sue Cadman, Biomedical Scientist.
The laboratory is located within the Clinical Research Unit and entry to the laboratory facilities requires an electronic security pass. The entire unit is locked out of office hours and is not accessible.

14. What will happen to the samples at the end of the research? Please tick all that apply and give further details.

☐ Transfer to research tissue bank

(If the bank is in England, Wales or Northern Ireland the institution will require a licence from the Human Tissue Authority to store relevant material for possible further research.)

☐ Storage by research team pending ethical approval for use in another project

(Unless the researcher’s institution holds a storage licence from the Human Tissue Authority, or the tissue is stored in Scotland, or it is not relevant material, a further application for ethical review should be submitted before the end of this project.)
ANNEX 2

Storage by research team as part of a new research tissue bank

(Your institution will require a licence from the Human Tissue Authority if the bank will be storing relevant material in England, Wales or Northern Ireland. A separate application for ethical review of the tissue bank may also be submitted.)

☒ Storage by research team of biological material which is not “relevant material” for the purposes of the Human Tissue Act
☐ Disposal in accordance with the Human Tissue Authority’s Code of Practice
☐ Other
☐ Not yet known

Please give further details of the proposed arrangements:

Samples will be stored at -80 degrees centigrade within the laboratory until analysed. We propose to conduct a further interventional study following the completion of our observational study. Subject to ethical approval, further testing of the stored samples from may be undertaken, should factors be identified as part of our second study which were not examined initially. Consent for this possibility will be explicitly sought from patients as part of consent for the observational study.
### PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.

<table>
<thead>
<tr>
<th>Research site</th>
<th>Investigator/ Collaborator/ Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institution name</td>
<td>Title</td>
</tr>
<tr>
<td>Department name</td>
<td>First name/ Initials</td>
</tr>
<tr>
<td>Street address</td>
<td>Surname</td>
</tr>
<tr>
<td>Town/city</td>
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<td>Post Code</td>
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<td>Dr CD Griffiths</td>
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Date: 19/04/2011

Reference: 11/WM/0102

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<tr>
<td>Contact</td>
<td>Dr M Price</td>
</tr>
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</table>

| Post Code   | DY8 5PD                          |
| Institution | Kingswinford Medical Practice    |
| Department  |                                 |
| Street      | Standhills Road                  |
| City        | Kingswinford                     |
| Code        | DY6 8DN                          |
| Contact     | Dr V Smart                       |

| Post Code   | DY3 3UH                          |
| Institution | The Ridgeway Surgery             |
| Department  |                                 |
| Street      | 175 The Ridgeway                 |
| City        | Dudley                           |
| Code        |                                 |
| Contact     | Dr K Dawes                       |

| Post Code   | DY6 9HS                          |
| Institution | Moss Grove Surgery               |
| Department  |                                 |
| Street      | 15 Moss Grove                    |
| City        | Kingswinford                     |
| Code        |                                 |
| Contact     | Dr S Parnell                     |

| Post Code   | B63 4WD                          |
| Institution | Halesowen Medical Practice       |
| Department  | St Margaret's Well Surgery       |
| Street      | 2 Quarry Lane                    |
| City        | Halesowen                        |
| Code        |                                 |
| Contact     | Dr J Darby                       |
PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.

9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

   - Will be held by the main REC or the GTAC (as applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
   - May be disclosed to the operational managers of review bodies, or the appointing authority for the main REC, in order to check that the application has been processed correctly or to investigate any complaint.
   - May be seen by auditors appointed to undertake accreditation of RECs.
   - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

11. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency’s statutory responsibilities.

12. I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee’s final opinion or the withdrawal of the application.

Contact point for publication (Not applicable for R&D Forms)

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.
Access to application for training purposes (Not applicable for R&D Forms)
Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by dr george hirsch on 17/03/2011 14:05.

Job Title/Post: Research Fellow
Organisation: Dudley Group of Hospitals NHS Foundation Trust
Email: gandnhirsch@tiscali.co.uk
Signature: ........................................................
Print Name: George Hirsch
Date: 17/03/2011 (dd/mm/yyyy)
D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.

7. I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Signature: ..............................................................

Print Name:

Post: Research and Development Manager

Organisation: Dudley Group of Hospitals NHS Foundation Trust

Date: 17/03/2011 (dd/mm/yyyy)
### D3. Declaration for student projects by academic supervisor(s)

1. I have read and approved both the research proposal and this application. I am satisfied that the scientific content of the research is satisfactory for an educational qualification at this level.

2. I undertake to fulfil the responsibilities of the supervisor for this study as set out in the Research Governance Framework for Health and Social Care.

3. I take responsibility for ensuring that this study is conducted in accordance with the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research, in conjunction with clinical supervisors as appropriate.

4. I take responsibility for ensuring that the applicant is up to date and complies with the requirements of the law and relevant guidelines relating to security and confidentiality of patient and other personal data, in conjunction with clinical supervisors as appropriate.

#### Academic supervisor 1

| Signature: | ............................................................................................................... |
| Print Name: | Dr Rainer Klocke |
| Post: | Consultant Rheumatologist |
| Organisation: | Dudley Group of Hospitals NHS Foundation Trust |
| Date: | 17/03/2011 (dd/mm/yyyy) |
Chairman: Dr S Bowman  
Co-ordinator: Mrs Rosa Downing

Date: 17 May 2011

Dr George Hirsch  
Clinical Research Unit, 1st floor,  
North Wing Russells Hall Hospital  
Dudley, West Midlands  
DY1 2HQ

Dear Dr Hirsch

Study title: An observational study of somatic and psychometric factors predicting response to intra-articular corticosteroid injection in primary and secondary osteoarthritis of the knee

REC reference: 11/WM/0102

Thank you for your letter of 10 May 2011, responding to the Committee’s request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).
Non-NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

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Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

11/WM/0102 Please quote this number on all correspondence

With the Committee’s best wishes for the success of this project

Yours sincerely

Dr Simon Bowman
Chair

Enclosures: “After ethical review – guidance for researchers” SL-AR2

Copy to: Mrs Margaret Marriott, Dudley Group of Hospitals NHS Foundation Trust

[Signature]
Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please enter a short title for this project (maximum 70 characters)
Predictors of response to steroid injection in knee arthritis

1. Is your project research?
☐ Yes  ☐ No

2. Select one category from the list below:
☐ Clinical trial of an investigational medicinal product
☐ Clinical investigation or other study of a medical device
☐ Combined trial of an investigational medicinal product and an investigational medical device
☐ Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
☐ Basic science study involving procedures with human participants
☐ Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
☐ Study involving qualitative methods only
☐ Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
☐ Study limited to working with data (specific project only)
☐ Research tissue bank
☐ Research database

If your work does not fit any of these categories, select the option below:
☐ Other study

2a. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?
☐ Yes  ☐ No

2b. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation?
☐ Yes  ☐ No
b) Will you be taking new human tissue samples (or other human biological samples)?
☐ Yes  ☐ No
c) Will you be using existing human tissue samples (or other human biological samples)?
☐ Yes  ☐ No

3. In which countries of the UK will the research sites be located? (Tick all that apply)
☑️ England
3a. In which country of the UK will the lead NHS R&D office be located:

- England
- Scotland
- Wales
- Northern Ireland
- This study does not involve the NHS

4. Which review bodies are you applying to?

- NHS/HSC Research and Development offices
- Social Care Research Ethics Committee
- Research Ethics Committee
- National Information Governance Board for Health and Social Care (NIGB)
- Ministry of Justice (MoJ)
- National Offender Management Service (NOMS) (Prisons & Probation)

For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.

5. Will any research sites in this study be NHS organisations?

- Yes
- No

5a. Do you want your NHS R&D application(s) to be processed through the NIHR Coordinated System for gaining NHS Permission?

- Yes
- No

If yes, you must complete and submit the NIHR CSP Application Form immediately after completing this project filter, before proceeding with completing and submitting other applications.

6. Do you plan to include any participants who are children?

- Yes
- No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

- Yes
- No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the NIGB Ethics and Confidentiality Committee to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

- Yes
- No
9. Is the study or any part of it being undertaken as an educational project?

- Yes  - No

Please describe briefly the involvement of the student(s):
Student will act as principal investigator.
Student will conduct baseline appointments, including informed consent, assessment of inclusion and exclusion criteria and baseline investigations, entry and handling of data.

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

- Yes  - No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

- Yes  - No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

- Yes  - No
### Short title and version number:
Predictors of response to steroid injection in knee arthritis

### PART A: Core study information

#### 1. ADMINISTRATIVE DETAILS

**A1. Full title of the research:**
An investigation of psychological and other predictors of pain reduction to open-label corticosteroid injection in primary and secondary osteoarthritis of the knee.

#### A2-1. Educational projects

**Name and contact details of student(s):**

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<tbody>
<tr>
<td>Title</td>
</tr>
<tr>
<td>Dr</td>
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<tr>
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<td>Post Code</td>
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<td>Telephone</td>
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</tbody>
</table>

Give details of the educational course or degree for which this research is being undertaken:

**Name and level of course/ degree:**
PhD

**Name of educational establishment:**
University of Manchester (in co-operation with MRC-ARUK Centre for Musculoskeletal ageing)
Please state which academic supervisor(s) has responsibility for which student(s):

A copy of a current CV for the student and the academic supervisor (maximum 2 pages of A4) must be submitted with the application.

A2-2. Who will act as Chief Investigator for this study?

☐ Student
☐ Academic supervisor
☐ Other

A3-1. Chief Investigator:

Title Forename/Initials Surname  
Dr George Hirsch

Post  
Research Fellow in Rheumatology

Qualifications  
BM BCh MRCP(UK)

Employer  
Dudley Group NHS Foundation Trust

Work Address  
Clinical Research Unit, 1st floor,  
North Wing, Russells Hall Hospital  
Dudley

Post Code  
DY1 2HQ

Work E-mail  
hirsch.george@dgh.nhs.uk

* Personal E-mail  
gandnhirsch@tiscali.co.uk

Work Telephone  
01384244807

* Personal Telephone/Mobile  
07791441269

Fax  
01384244808

* This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.

A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?

This contact will receive copies of all correspondence from REC and R&D reviewers that is sent to the CI.
Some studies may have straightforward ethical or other issues that can be identified. A35. If your work does not fit any of these categories, select the option below:

- New research
- Development
- Pilot study
- Studies with a new method
- Studies with a new tool
- Studies of public health relevance
- Other

A32. If Yes, please explain.

A2. What is the total participant dose from all the exposures in A1 and/or B1, and what component of this is the dose and risk assessment should be set out below.

A1. Are radioactive materials used in your study?

☐ Yes ☐ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, this summary will be published on the website of the National Research Ethics Service following the ethical review.

People with x-ray changes of knee osteoarthritis (OA) vary greatly in the level of symptoms and limitations they report and this is difficult to predict from the severity of the x-rays. Those who do report significant pain also vary greatly in the...
level of pain relief they report following the commonly used treatment of intra-articular corticosteroid injections (IACI).

We propose an observational study of subjects receiving corticosteroid injections for primary and secondary osteoarthritis (OA) of the knee, with the aim of determining factors predictive of response to injection. Injections will be performed according to usual clinical practice. Participants will be assessed for a variety of physical and psychological aspects involving x-rays, ultrasound, blood and urine tests and questionnaires at the beginning of the study. Ultrasound (US) will be used to check the position of injections once performed.

The variables will be examined statistically for their ability to predict pain relief at 3 and 9 weeks. The particular focus of our research is to further clarify the suggested effect on treatment outcomes of participants’ perceptions of the effectiveness of the particular treatment and also the level to which they feel that they have made an active decision to receive that particular treatment (in this case corticosteroid injections).

A6-2. Summary of main issues. Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, R&D office or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

An observational study raises few ethical issues. The main impositions on patients will be questionnaire load and the requirement to provide an additional serum and urine sample. They will require 3 x-ray views of the knee. It is likely that at least two of these would be acquired as part of standard care. The total additional exposure to radiation, even assuming all 3 views were required, would be unlikely to be in excess of the equivalent of two days of natural background radiation (see radiation assessment). Beyond this, their clinical care will remain as normal.

The anatomical approach chosen for injections will not be standardised, since selection of a particular technique may have importance for outcomes that can be demonstrated in the study, but the approach chosen in each case will be recorded. Composition of injections will be standardised and will reflect those used in normal practice. Our injection protocol will differ from normal practice in two respects. The first is that we will also include 2 ml of atmospheric air within the injection mixture in order to act as contrast for a mini air-arthrogram and the second that we will perform a brief US examination after injection to detect the air. In the papers describing this technique (Qvistgaard, Fredberg, Koski), over 1400 injections were performed without any recorded complications, neither did a search of all available databases (including NPSA) reveal any reports of complications arising from it.

Mini air-arthrography will allow us to determine whether injections have been placed in the intra-articular space or failed to enter the space. Following the injection, the ultrasound probe will be used to determine the position of the injection. We will explain to patients in advance about this extra step, stating that the purpose is to ‘show where the injection distributes to’. We will further state that we will not explain the results of this test to them in detail, in case this information influences what they report later.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. Please tick all that apply:

- [ ] Case series/ case note review
- [ ] Case control
- [x] Cohort observation
- [ ] Controlled trial without randomisation
- [ ] Cross-sectional study
- [ ] Database analysis
- [ ] Epidemiology
- [ ] Feasibility/ pilot study
- [ ] Laboratory study
- [ ] Metanalysis
A10. What is the principal research question/objective? Please put this in language comprehensible to a lay person.

We wish to identify factors that allow clinicians to predict whether a patient is likely to have meaningful pain relief in response to corticosteroid injection to the knee at 3 and 9 weeks post injection. These factors will include psychological factors, x-rays, ultrasound scan appearances, blood and urine tests, factors related to the patient such as whether they have arthritis in other places, back pain or have high body weight. The effects of accuracy of injections will be tested with ultrasound.

A11. What are the secondary research questions/objectives if applicable? Please put this in language comprehensible to a lay person.

Determine whether the relationship between treatment control illness perceptions (beliefs about how much treatments can alter symptoms) and rate of response to injection is dependent upon (mediated by) the kind of motivation patients have for treatment.

Determine whether measures of psychological good and ill health (Subjective vitality, depression and anxiety) change following intra-articular steroid injection.

Determine whether response to corticosteroid injection is linked to evidence of inflammation in the joint, as measured by concentrations of Interleukin-6(IL-6), Interleukin-1(IL-1) and Tumour Necrosis Factor-α(TNF-α) in the joint fluid or fluid white cell count (WCC).

Determine how psychological factors may interact with physical factors such as x-rays, ultrasound appearances or blood tests in predicting the reduction of pain after a corticosteroid injection.

A12. What is the scientific justification for the research? Please put this in language comprehensible to a lay person.

Osteoarthritis is the commonest form of arthritis in the developed world. Its prevalence increases steadily with age and will become even more widespread as the proportion of older people in our population grows. One of the defining features of the condition is the presence of characteristic changes on x-rays. In surveys of people over 65, up to 40% were found to have changes characteristic of OA present on knee x-rays but it was also observed that only around 12% of people in the survey were suffering from significant knee pain. Why some people suffer severe pain and limitation in their activities while in a significant proportion of the population the condition gives rise to few or no symptoms and is apparently compatible with healthy musculoskeletal ageing and leading normal lives is, so far, unexplained and an enigmatic feature of OA.

Amongst those with established symptomatic knee OA, injections of corticosteroid into the joint (Intra-articular corticosteroid injections, IACI) are currently widely used internationally for the treatment of knee pain. For many people this can delay or reduce the need for more invasive interventions such as joint replacement surgery. However, it is further recognized that individuals receiving this treatment report very varied results, both in terms of reduction of pain and duration of response. Despite the use of IACI for several decades, this variation of responses is also unexplained and robust clinical predictors of which individuals respond to injections better have not been identified, beyond a suggestion in one study of better response in those with excess fluid on the knee (a.k.a. effusion).

The observation that people with knee effusion may respond better to injection could relate to inflammation in the joint. Since steroids are usually used to reduce inflammation, it could be suggested that this is how they might work in OA. If this is the case, then a better response in the case of patients showing signs of inflammation in the joint might be expected.

A further group of characteristics that might affect reported outcomes is that of psychological factors. It is known that psychological characteristics have significant effects on the levels of pain that individuals report and also their response to some pain relieving procedures. This aspect had not been explored in the context of IACI for knee OA. However, we conducted a pilot study of 32 subjects (recruited between June- November 2011) which suggested a link between psychological characteristics and pain reduction following injection. Psychological characteristics assessed included subjects’ Illness perceptions (otherwise known as Health Beliefs; sets of beliefs people have about the characteristics of their illness) and Pain catastrophizing (negative thoughts and feelings people have when experiencing or thinking about pain). We assessed Illness Perceptions using the Revised Illness Perception Questionnaire (IPQR) and the Pain Catastrophizing Questionnaire (PCS).
We found that higher ratings for 'treatment control illness perceptions' (i.e. how strongly subjects reported beliefs that treatment could improve their symptoms) were associated with higher rates of response. High ratings for 'Pain Catastrophizing' (a highly negative profile of thoughts in response to pain) also showed a trend towards association with a lower response rate.

The small size of our sample, however, did not permit us to determine whether the effects of these factors were still significant after correcting for other subject characteristics. A larger study will allow us to provide better evidence for the link between individual psychological factors and response to injection by allowing us to correct for the effects both of other psychological factors examined and physical factors, as well as pursuing some additional novel lines of inquiry.

We propose to examine the role of an individual's motivation for treatment, in particular so called 'autonomous' versus 'controlled' motivation as a potential predictor of response. An autonomous decision is one which someone takes in the belief that it is the best possible and most desirable option for them, according to their own internal values and in the absence of any external pressure. By contrast, 'controlled motivation' describes a situation in which people may take decisions due to factors such as perceived pressure from family members or healthcare providers, the opinions of others or financial or social requirements.

There is compelling evidence to show that autonomous motivation for health behaviours such as diabetes control, medication adherence, smoking cessation and weight loss is predictive of better outcomes. We hypothesize that those subjects with the strongest treatment control beliefs will also be those who have the highest levels of autonomous motivation; thus those with higher levels of autonomous motivation for treatment will also report better outcomes than those with other forms of motivation.

Levels of autonomous versus controlled motivation for healthcare treatments can be measured using the Treatment Self Regulation Questionnaire (TSRQ) and the individual's perception of how much the treatment environment supports their autonomous decision making by the Healthcare Climate Questionnaire (HCCQ). We propose to use these validated questionnaires in our study.

It is known that physical symptoms influence psychological health. We propose to use subjective vitality as a measure of psychological good health (using the subjective vitality scale; SVS) and depression and anxiety as measures of psychological ill health (as assessed by the Arthritis Impact Measurement Scale 2; AIMS2). Changes in these measures over the course of the study will be compared with changes in knee symptoms to determine whether successful treatment of symptoms also leads to improvement in psychological health.

Lastly and importantly, both motivational factors and illness perceptions have been shown to be modifiable by psychological interventions and these changes linked to improved health outcomes. Proof of a link between psychological factors and response to injection would, therefore, prepare the way for further research attempting to use such interventions to improve the outcomes of individuals in whom psychological factors predict poor response to injection.

We anticipate that this project will have implications beyond the area of injection therapies alone. In other areas of OA therapy, notably interventions using exercise and physiotherapy, weight loss and physical devices such as knee braces and insoles, the long term effectiveness of treatments and of lifestyle modifications is restricted by the problems of people not engaging with or continuing with them. We would anticipate that the same potentially modifiable variations in individuals' autonomy and illness perceptions will have equal if not more important effects on these behaviours and that understanding this relationship will assist in maintaining continued health and independence in the face of musculoskeletal ageing.

**A13. Please summarise your design and methodology.** It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.

Subjects with knee osteoarthritis with whom injection has been discussed as an appropriate treatment option will be identified by clinicians within the rheumatology and orthopaedic departments with Dudley Group NHS Foundation Trust. The study will be discussed with them and written information given including the details of the study, procedures and samples required, number of visits and length of follow-up. Permission will be sought to contact them by telephone to discuss the study further. Alternatively, patients may use the reply slip provided with the patient information sheet. For those that express an interest in participating after having adequate time to study the information provided, a baseline visit and consent procedure will be organised immediately prior to their injection. For those who do not wish to participate, an appointment will be arranged to perform injection only.

At the baseline visit, participants will be asked to sign a consent form prior to any study procedures, after being given the opportunity to discuss the requirements of the study and ask questions. Consent will be sought for a urine sample and venous blood sample to be taken at baseline and at 3 weeks and for these to be stored until the end of the study. Consent will also be sought for a sample of joint (synovial) fluid to be taken at the time of injection if possible,
and for this to be stored until the end of the study. Consent will be sought for x-rays of the knee in 3 views, unless these have been taken within the last 6 months, and for ultrasound assessment of the knee immediately before and after the injection.

Following consent, patient demographics such as age, Body Mass Index (BMI) and smoking status and relevant medical comorbidities will be recorded. Relevant comorbidities include back pain, contralateral knee OA, hip OA, diabetes. Where significant pain outside the knee is present, participants will be asked indicate where this pain is and to estimate its severity using a standardised visual analogue scale.

Participants will be asked to complete several questionnaires at baseline. The first of the these will be a Western Ontario and McMaster Osteoarthritis Index (WOMAC) score, together with a single additional measure of a patient's global impression of the impact of their knee arthritis and a second for overall knee pain. The WOMAC is an internationally recognized scale for judging the impact of the severity of symptoms in arthritis in various situations. The psychological questionnaires include measures of how individuals react to pain (PCS; 13 questions) and what they believe about their illness (IPQR; 38 questions). Psychological wellbeing will be assessed by the Subjective Vitality Scale (SVS; 6 questions) and psychological ill-health by questionnaires to identify signs of depression or anxiety (AIMS2; 10 questions in total). Lastly, two questionnaires will examine the qualities of individuals' motivation for treatment (T SRQ; 15 questions) and whether they see their treatment environment as supporting them in making independent decisions (HCCQ; 6 questions).

Participants who also have Rheumatoid Arthritis will have a standard assessment of their disease activity (DAS28), which includes a brief examination of 28 joints for signs of inflammation and a single question about the level of symptoms currently caused by their arthritis.

Injections will be performed immediately following ultrasound assessment by a clinician blinded to ultrasound findings, using an injection of standard composition and including 2 ml of air, administered by whichever technique of injection they feel is appropriate. The approach used will be recorded. Removal of synovial fluid (aspiration) will routinely precede injection and, as in normal clinical practice, injecting clinicians will remove all synovial fluid they can. Where synovial fluid has been removed, up to 5 ml will stored as per consent. Following injection ultrasound will be used to confirm whether or not the injection has accurately entered the joint by using the air as a marker. Participants will not be advised of the findings, as specified in A6-2. Participants will be advised to rest for 24 hours following the procedure, as in our standard clinical practice.

Repeat assessments of outcomes will be performed at 3 and 9 weeks and repeat blood testing and urine testing will be undertaken at 3 weeks, as detailed in the consent. Subjects will be invited to attend for a review at the hospital at 3 weeks (+/- 3 days), at which repeat blood and urine testing will be performed. Subjects will be asked to complete an outcome questionnaire comprising physical outcomes (WOMAC, patient global assessment), Psychological outcomes (Subjective Vitality Scale and AIMS2 depression and anxiety subscales), a single question about the frequency of medication use and the outcome section of the Goal Content Questionnaire for Arthritis.

Participants who have Rheumatoid Arthritis will have a further DAS28 assessment at this point. Subjects unable to attend review at this point will be invited to return a questionnaire by post. All questionnaires for the final review at 9 weeks can be returned by post (comprising WOMAC, patient global assessment, Subjective vitality scale, AIMS2 subscales and medication questionnaire).

Factors being examined as potential predictors of response will be examined by correlation with whether or not subjects respond to corticosteroid injection at 3 and 9 weeks. The main definition of response is a reduction of 40% in pain score from baseline to each of these time-points.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- [x] Design of the research
- [ ] Management of the research
- [ ] Undertaking the research
- [ ] Analysis of results
- [ ] Dissemination of findings
- [ ] None of the above
Give details of involvement, or if none please justify the absence of involvement.
Members of our patient support groups have been consulted on the information about the study given to patients and the consent forms. Participants in the pilot study have advised about organizing study visits to maximise convenience to those participating in the study. Patient information sheets have been reviewed at several stages by lay-people to ensure that they are clearly understandable.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- Blood
- Cancer
- Cardiovascular
- Congenital Disorders
- Dementias and Neurodegenerative Diseases
- Diabetes
- Ear
- Eye
- Generic Health Relevance
- Infection
- Inflammatory and Immune System
- Injuries and Accidents
- Mental Health
- Metabolic and Endocrine
- Musculoskeletal
- Neurological
- Oral and Gastrointestinal
- Paediatrics
- Renal and Urogenital
- Reproductive Health and Childbirth
- Respiratory
- Skin
- Stroke

Gender: Male and female participants
Lower age limit: 40 Years
Upper age limit: No upper age limit

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

Primary Knee OA (as defined by ACR criteria)
OR Patients with Rheumatoid Arthritis with secondary osteoarthritis (as defined by persistent knee pain characteristic of OA for greater than 6 weeks and radiographic changes consistent with OA)
age above 40
clinician suggesting intra-articular steroid injection as a form of management
WOMAC pain subscale score above 20mm at baseline
A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

lack of informed consent to the study

previous corticosteroid injection within the preceding 3 months (intra-articular or intra-muscular)
Co- Existing Inflammatory Arthritis other than Rheumatoid Arthritis
use of oral steroid >7.5mg prednisolone or equivalent
existent diagnosis of fibromyalgia or other chronic widespread pain disorder
Patients with contraindication to intra-articular steroid injection will also be excluded such as those with bleeding
      diathesis, active current infection, chronic leg ulcer, uncontrolled diabetes or uncontrolled hypertension, allergy to
      triamcinolone or lignocaine preparation.

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. These include seeking consent, interviews, non-clinical observations and use of questionnaires.

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

<table>
<thead>
<tr>
<th>Intervention or procedure</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent</td>
<td>1</td>
<td>0</td>
<td>10min</td>
<td>Research Fellow, Research Nurses Clinical Research Unit, RHH</td>
</tr>
<tr>
<td>Complete baseline demographic information</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>Research Fellow, Research Nurses Clinical Research Unit, RHH</td>
</tr>
<tr>
<td>1. Completion of outcome questionnaire (WOMAC, patient global VAS, SVS, AIMS)</td>
<td>3</td>
<td>0</td>
<td>20</td>
<td>Patients. Initial questionnaire will be filled out at baseline in Clinical Trials Unit, RHH. Second and third questionnaires can be filled out by patients at their convenience at the appropriate time point and returned to the department.</td>
</tr>
<tr>
<td>2. GCQ for arthritis (goals at baseline, outcome at week 3), medication use (3 and 9)</td>
<td>1</td>
<td>0</td>
<td>45</td>
<td>min</td>
</tr>
<tr>
<td>completion of psychological questionnaires (IPQR, PCS, TSRQ, HCCQ)</td>
<td>1</td>
<td>0</td>
<td>45</td>
<td>Clinical Trials Unit, RHH.</td>
</tr>
</tbody>
</table>

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

<table>
<thead>
<tr>
<th>Intervention or procedure</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray of knee to be injected from 3 directions: Anterior-Posterior, lateral and 'sky-line'-unless available already and within six month of intervention. These will occur on ONE occasion only.</td>
<td>3</td>
<td>2</td>
<td>20</td>
<td>Radiology Dept, Russells Hall Hospital</td>
</tr>
</tbody>
</table>
The Research Nurse
Dudley Group NHS Foundation Trust
Research Fellow/ R. Klocke

Consideration should be given to the specific objectives of the exposure, (including identification of potential participants) for themselves?

Please enclose a copy of relevant documents.

Synovial fluid samples will be collected by the research fellow at the time of aspiration. Aspiration itself will be

The ability of individual variables to predict the response to corticosteroid injection at 3 weeks, as defined by WOMAC

Determine how psychological factors may interact with physical factors such as x-rays, ultrasound appearances or

Upper age limit:

Lower age limit:

The main burden for patients is the completion of questionnaires at the first visit and being required to attend for a

We found that higher ratings for 'treatment control illness perceptions' (i.e. how strongly subjects reported beliefs that

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

☐ Yes  ☐ No

A21. How long do you expect each participant to be in the study in total?

9 weeks from intervention to final assessment.

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

The main burden for patients is the completion of questionnaires at the first visit and being required to attend for a second visit which is not part of their normal care.

They will also be required to provide two blood samples and two urine samples that would not be required under normal circumstances, and potentially up to three x-rays of the affected knee, although in practice it is likely that at least two of these x-rays will already have been taken as part of their standard case. Ultrasound scan will be undertaken immediately prior to injection and a rapid confirmation of the position of injection immediately after it.

We will aim to minimise the financial burden and inconvenience to patients of a further visit by reimbursing their travel costs for the second visit.

The risk of infection posed by the injection procedure itself is no greater than that posed by standard care and is quoted to be 1/150000 injections.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

☐ Yes  ☐ No

A24. What is the potential for benefit to research participants?

The main benefit for patients is receiving an injection to reduce their symptoms. The fast-track system of referral we propose from orthopaedics and rheumatology clinics may allow them to receive this more quickly than they would do as part of normal clinical care.

Because of additional contact at three weeks, they will also be subject to closer surveillance than normal in the case of complications occurring.

In cases of poor clinical response to injection, it will be possible after collecting week 9 data to disclose information relating to accuracy of injection to clinicians referring the patient. This would allow those that wished to refer the patient (through normal clinical pathways) for injection under imaging guidance, based on the currently accepted premise that accurate injection might improve response to injection.
A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.

Since this intervention is given as part of usual care, further provision for repeat injections will be made by the team normally delivering patient care, if deemed appropriate.

A26. What are the potential risks for the researchers themselves? (if any)

None

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used? For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).

Patients will be identified by the clinicians referring patients for injection from general service clinics (rheumatologists, orthopaedic surgeons, orthopaedic nurse consultant). At the time of referral, the study will be discussed with them and a written Patient Information Sheet given to them. It will be made clear to patients during this discussion that expression of interest in the study does not in any way compel them to take part and that their treatment is not dependent on them doing so.

Referrals will be accepted from rheumatology and orthopaedic departments within the Dudley Group NHS Foundation Trust.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

☐ Yes  ☒ No

Please give details below:

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

☐ Yes  ☐ No

A29. How and by whom will potential participants first be approached?

Initial approach will be made by clinicians referring patients for injection, written information given and permission sought to contact them by telephone. Telephone contact will be made by the researcher in order to discuss further details and arrange an appointment if agreed by the patient. It will be clearly explained to patients that arranging an appointment does not constitute giving consent to participate and that if they change their minds about taking part in the study prior to attending a baseline appointment, an injection will be performed as standard without any questions being asked and without prejudicing their care.

In cases in which patients do not wish to receive injection, this information will be conveyed to the referrer. In cases in which patients wish to have injection but do not wish to participate in research, an appointment will be arranged to perform injection without enrolment to the study.

A30-1. Will you obtain informed consent from or on behalf of research participants?

☒ Yes  ☐ No
If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

Consent will be taken in written form by the research fellow. Written information, in any cases where it has not been given to the patient by the referring clinician, will be sent to potential participants to ensure that they have the chance to read it in full a minimum of 24 hours before deciding whether they wish to consider participating. The full details will be explained again verbally and any questions answered prior to consent being signed.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30.2. Will you record informed consent (or advice from consultees) in writing?

☐ Yes  ☐ No

A31. How long will you allow potential participants to decide whether or not to take part?

Participants will have the time between the initial proposal and the time of their injection to decide on whether to participate, since their baseline appointment will take place immediately before their injection. This period will be no less than 24 hours. Written information will facilitate them in making an informed decision concerning participation prior to their baseline visit.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

☐ Yes  ☐ No  ☐ Not Known

A33.1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? (e.g. translation, use of interpreters)

Patients will not be enrolled if unable to understand spoken English. (Since the complete set of questionnaires are validated in English language only)

Where unable to read written information in English, this will be explained fully to the patient in a verbal form.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

If such an eventuality should arise, patients will be contacted by telephone, although it is difficult to imagine this situation arising, given that only one procedure will occur at the beginning of the study. The intervention is given frequently in routine clinical care and has a proven safety record.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? Tick one option only.

☐ The participant and all identifiable data or tissue collected would be withdrawn from the study. Is not identifiable to the research team may be retained.

☐ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried

15 104354/365423/14/722
out on or in relation to the participant.

- The participant would continue to be included in the study.
- Not applicable – informed consent will not be sought from any participants in this research.
- Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

If you plan to retain and make further use of identifiable data/tissue following loss of capacity, you should inform participants about this when seeking their consent initially.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? (Tick as appropriate)

- Access to medical records by those outside the direct healthcare team
- Electronic transfer by magnetic or optical media, email or computer networks
- Sharing of personal data with other organisations
- Export of personal data outside the EEA
- Use of personal addresses, postcodes, faxes, emails or telephone numbers
- Publication of direct quotations from respondents
- Publication of data that might allow identification of individuals
- Use of audio/visual recording devices
- Storage of personal data on any of the following:
  - Manual files including X-rays
  - NHS computers
  - Home or other personal computers
  - University computers
  - Private company computers
  - Laptop computers

Further details:

Patient identifiable data will be recorded on baseline proforma only, stored under locked file in CRU and not stored electronically.

Non-identifiable data (outcome assessment data etc.) will be stored on encrypted laptop computer, under identification number assigned to each patient for the study. However, no personal or patient identifiable data will be stored in this manner.

A37. Please describe the physical security arrangements for storage of personal data during the study?

Paper records will be stored in locked filing cabinets within the trials unit. Filing cabinets keys are protected by combination key-safe. The offices are accessible by the research team during the day by way of a locked door operated by personal electronic security cards with restricted access and are constantly occupied. Both offices and the unit are locked outside office hours.

Non-identifiable information only will be stored electronically in encrypted manner on computer terminal within these office hours.
A38. How will you ensure the confidentiality of personal data? *Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

Patients will be allocated a unique identification number at baseline and this used to identify their clinical data throughout the study, outside the core record of participants.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Patient personal data will only be recorded on baseline proforma, which will remain in locked filing cabinet within a secure area of the Clinical Research Unit. Only the research fellow will have access to this data. Personal data will not be stored electronically.

### Storage and use of data after the end of the study

**A41. Where will the data generated by the study be analysed and by whom?**

Analysis will be undertaken within the clinical trials department at Russells Hall Hospital by the research fellow under guidance from Peter Nightingale, Statistician at University Hospitals Birmingham and statisticians at the ARUK clinical epidemiology unit in Manchester.

**A42. Who will have control of and act as the custodian for the data generated by the study?**

<table>
<thead>
<tr>
<th>Title</th>
<th>Forename/Initials</th>
<th>Surname</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr</td>
<td>George</td>
<td>Hirsch</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post</th>
<th>Research Fellow Rheumatology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualifications</td>
<td>BA BM BCh MRCP(UK)</td>
</tr>
<tr>
<td>Work Address</td>
<td>Clinical Research Unit</td>
</tr>
<tr>
<td></td>
<td>Russells Hall Hospital</td>
</tr>
<tr>
<td></td>
<td>Dudley</td>
</tr>
<tr>
<td>Post Code</td>
<td>DY1 2HQ</td>
</tr>
<tr>
<td>Work Email</td>
<td><a href="mailto:hirsch.george@dgh.nhs.uk">hirsch.george@dgh.nhs.uk</a></td>
</tr>
<tr>
<td>Work Telephone</td>
<td>01384244807</td>
</tr>
<tr>
<td>Fax</td>
<td>01384244808</td>
</tr>
</tbody>
</table>

**A43. How long will personal data be stored or accessed after the study has ended?**

- [ ] Less than 3 months
- [ ] 3 – 6 months
- [ ] 6 – 12 months
- [ ] 12 months – 3 years
- [x] Over 3 years

*If longer than 12 months, please justify:*

We wish to apply for storage of personal data for a period of five years to allow us to contact patients to participate in further projects, as stated in the consent form. Further potential projects in consideration involve qualitative interviews to examine the formative influences on patients’ illness perceptions and also a trial of the effects of psychological intervention on illness perceptions, with the aim of improving outcomes. Both of these projects would be most successful if targeted to patients with particular profiles of illness perceptions (information which we will accumulate as part of this project).
A44. For how long will you store research data generated by the study?

| Years: | 5 |
| Months: | |

A45. Please give details of the long term arrangements for storage of research data after the study has ended. Say where data will be stored, who will have access and the arrangements to ensure security.

Study data will be retained in the secure archive facility in the Clinical Research Unit. Access will be obtained by members of the research team. Keys to the archive are retained within a key-safe within the CRU offices, the security arrangements of which are laid out in section A37.

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

- Yes  
- No

If Yes, please give details. For monetary payments, indicate how much and on what basis this has been determined. Reimburse transport costs to second appointment equivalent to parking costs or return trip by public transport.

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

- Yes  
- No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

- Yes  
- No

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A49-1. Will you inform the participants’ General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

- Yes  
- No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

- Yes  
- No

It should be made clear in the participant’s information sheet if the GP/health professional will be informed.

---

A50. Will the research be registered on a public database?

The Department of Health's Research Governance Framework for Health and Social Care and the research
governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that “every clinical trial must be registered on a publicly accessible database before recruitment of the first subject”; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

Please give details, or justify if not registering the research.

This study has been adopted by the MRC-ARUK centre for Musculoskeletal ageing (Birmingham-Nottingham-Dudley).

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? Tick as appropriate:

- [ ] Peer reviewed scientific journals
- [ ] Internal report
- [ ] Conference presentation
- [ ] Publication on website
- [ ] Other publication
- [ ] Submission to regulatory authorities
- [ ] Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- [ ] No plans to report or disseminate the results
- [ ] Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

We will not be using identifiable data

A53. Will you inform participants of the results?

- [ ] Yes
- [ ] No

Please give details of how you will inform participants or justify if not doing so.

A lay summary of results will be made available to patients who have participated in the research and sent to them on completion of the study.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? Tick as appropriate:

- [ ] Independent external review
- [ ] Review within a company
- [ ] Review within a multi-centre research group
- [ ] Review within the Chief Investigator's institution or host organisation
- [ ] Review within the research team
- [ ] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:

Review has been conducted according to formal process within the sponsor's organisation and by Professor Janet Lord, representing the MRC-ARUK centre for musculoskeletal ageing. No questions were raised regarding our
hypotheses or assessment methods.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? Tick as appropriate:

- Review by independent statistician commissioned by funder or sponsor
- Other review by independent statistician
- Review by company statistician
- Review by a statistician within the Chief Investigator’s institution
- Review by a statistician within the research team or multi–centre group
- Review by educational supervisor
- Other review by individual with relevant statistical expertise
- No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

Title: Forename/Initials Surname
Mr: Peter Nightingale

Department: Wellcome Trust Clinical Research Facility
Institution: University Hospitals Birmingham NHS Foundation Trust
Work Address: 1st Floor, Blue Zone
Queen Elizabeth Hospital
Birmingham

Post Code: B15 2TH
Telephone: 0121 472 1311, ext 2586
Fax
Mobile
E-mail: P.G.Nightingale@bham.ac.uk

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

Response as defined by 40% fall in WOMAC pain subscale from baseline values at week 3.

A58. What are the secondary outcome measures? (if any)

WOMAC responder status at 9 weeks (reduction of WOMAC pain sub-scale by 40% relative to baseline). Osteoarthritis Research Society International (OARSI) response at 3 and 9 weeks. This uses 100mm Visual Analogue Scale (VAS) measurements for pain, function (both of which can be extracted from the WOMAC scores) and patient global assessment. A response is defined as:

≥50% change in pain or function, accompanied by ≥20 absolute change in the same domain
OR improvement of 2 of 3 of:
1. pain ≥20% and absolute change ≥10
2. function ≥20% and absolute change ≥10
3. patient global assessment ≥20% and absolute change ≥10
A59. **What is the sample size for the research?** How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.

<table>
<thead>
<tr>
<th>Total UK sample size:</th>
<th>220</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total international sample size (including UK):</td>
<td>220</td>
</tr>
<tr>
<td>Total in European Economic Area:</td>
<td></td>
</tr>
</tbody>
</table>

Further details:

A60. **How was the sample size decided upon?** If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.

The power calculation for our study is based on data collected during our pilot and was performed by Mr Peter Nightingale, statistician at University Hospitals Birmingham. The calculation was performed based on the psychological and outcome data from the pilot study, using the initial sample of 32 patients. The calculations were based on the rate of WOMAC response, defined as a WOMAC change score >0.4. The observed response rate in the pilot study was 53%.

Initial analysis suggested that IPQR treatment control provided the best predictor of WOMAC response and that the next closest relationship was IPQR consequences, although this was not itself significant as a predictor.

The observed mean for treatment control was 18.1 (SD 2.8.)

The observed mean for consequences was 19.7 (SD 5.3)

The observed correlation between treatment control and consequences was -0.43

Odds ratio for WOMAC response was 1.439 for treatment control and 0.979 for consequences in a multivariable logistic regression analysis including both variables.

The sample size indicated to detect the effect of treatment control in univariable logistic regression analysis was 53.

For multivariable logistic regression, a sample size of 200 was found to be sufficient to detect an odds ratio of 0.9 for consequences in a forward logistic regression model in which treatment control was entered first and consequences entered as the second variable. A sample of 220 was chosen to allow for up to a 10% drop-out rate from the study.

A61. Will participants be allocated to groups at random?

- [ ] Yes
- [x] No

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

The ability of individual variables to predict the response to corticosteroid injection at 3 weeks, as defined by WOMAC response above, will be examined using univariate analysis. Factors suggested by univariate analysis to be associated with response will be entered into multivariable logistic regression analysis and their ability as independent predictors of response tested.

Structured equation modelling will be used to test a model in which the effect of individual autonomy is mediated by treatment control illness perceptions.

### 6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. Please include all grant co-applicants, protocol co-authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.

<table>
<thead>
<tr>
<th>Title</th>
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<th>Surname</th>
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<tbody>
<tr>
<td>Title Forename/Initials Surname</td>
<td>Mrs Chitra Ramful</td>
</tr>
<tr>
<td>Post</td>
<td>Research Nurse</td>
</tr>
<tr>
<td>Qualifications</td>
<td>Dudley Group of Hospitals NHS Foundation Trust</td>
</tr>
<tr>
<td>Employer</td>
<td>Clinical Research Unit, 1st Floor</td>
</tr>
<tr>
<td>Work Address</td>
<td>North Wing, Russells Hall Hospital</td>
</tr>
<tr>
<td>Post Code</td>
<td>DY01 02HQ</td>
</tr>
<tr>
<td>Telephone</td>
<td>01384244754</td>
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<td>01384244754</td>
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<tr>
<td>Mobile</td>
<td>013842444808</td>
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<tr>
<td>Work Email</td>
<td><a href="mailto:daljit.kaur2@dgh.nhs.uk">daljit.kaur2@dgh.nhs.uk</a></td>
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<tr>
<td>Title Forename/Initials Surname</td>
<td>Mrs Sue Cadman</td>
</tr>
<tr>
<td>Post</td>
<td>Biomedical Scientist</td>
</tr>
<tr>
<td>Qualifications</td>
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<tr>
<td>Work Email</td>
<td><a href="mailto:cadman@dgh.nhs.uk">cadman@dgh.nhs.uk</a></td>
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<tr>
<td>Title Forename/Initials Surname</td>
<td>Mrs Jackie Smith</td>
</tr>
<tr>
<td>Post</td>
<td>Senior Biomedical Scientist</td>
</tr>
<tr>
<td>Qualifications</td>
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<tr>
<td>Employer</td>
<td>Clinical Research Unit, 1st Floor</td>
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<tr>
<td>Work Address</td>
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<tr>
<td>Title Forename/Initials Surname</td>
<td>Dr Ruth Shave</td>
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<tr>
<td>Post</td>
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</table>
Title Dudley Group NHS Foundation Trust

Identifiable data or tissue already collected with consent would be used for research purposes.

Some studies may have straightforward ethical or other issues that can be identified. It is advisable to discuss the proposed research with the investigators/collaborators arising from harm to participants in the study.

A75

Please enclose a copy of relevant documents.

It should be made clear in the participant information that the research involves the collection of data. The sample size indicated to detect the effect of treatment control in univariable logistic regression analysis was 53.

The observation that people with knee effusion may respond better to injection could relate to inflammation in the joint. The particular focus of our research is to further clarify the suggested effect on treatment outcomes of participants with knee effusion.

If your work does not fit any of these categories, select the option below:

If Yes, will arrangements be made to notify the individuals concerned?

If Yes, say what arrangements will be made and give details of the support or counselling provided.

If so, will arrangements be made to notify the individuals concerned?

In which aspects of the research process have you actively involved, or will you involve, patients, service users, or carers?

What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee be established?

Publication of data that might allow identification of individuals would be disclosed in response to requests made under the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.

As detailed in section B9, unanticipated high CRP levels would warrant recall of the patient for clinical review, and the patient would be reviewed by a senior member of the rheumatology team.

Patients. Initial questionnaire will be filled out at the start of the study, and participants will be reviewed on the Clinical Research Unit within 24 hours as necessary.

If so, will arrangements be made to notify the individuals concerned?

If Yes, say what arrangements will be made and give details of the support or counselling provided.

In which aspects of the research process have you actively involved, or will you involve, patients, service users, or carers?

What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee be established?
Is the sponsor based outside the UK?
- Yes
- No

Under the Research Governance Framework for Health and Social Care, a sponsor outside the UK must appoint a legal representative established in the UK. Please consult the guidance notes.

A65. Has external funding for the research been secured?
- Funding secured from one or more funders
- External funding application to one or more funders in progress
- No application for external funding will be made

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1)?
- Yes
- No

Please give details of subcontractors if applicable.

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?
- Yes
- No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68. Give details of the lead NHS R&D contact for this research:

Title Forename/Initials Surname
- Mrs Margaret Marriott

Organisation
- Dudley Group NHS Foundation Trust

Address
- Clinical Research Unit, 1st Floor, North Wing, Russells Hall Hospital.
A69-1. How long do you expect the study to last in the UK?

Planned start date: 01/10/2012
Planned end date: 01/04/2014
Total duration:
Years: 1  Months: 6  Days: 0

A70. Definition of the end of trial, and justification in the case where it is not the last visit of the last subject undergoing the trial (1)

Final follow-up visit of last subject recruited to the trial.

A71-1. Is this study?

- Single centre
- Multicentre

A71-2. Where will the research take place? (Tick as appropriate)

- England
- Scotland
- Wales
- Northern Ireland
- Other countries in European Economic Area

Total UK sites in study 1

Does this trial involve countries outside the EU?

- Yes  
- No

A72. What host organisations (NHS or other) in the UK will be responsible for the research sites? Please indicate the type of organisation by ticking the box and give approximate numbers of planned research sites:

- NHS organisations in England 1
- NHS organisations in Wales
- NHS organisations in Scotland
- HSC organisations in Northern Ireland
- GP practices in England
- GP practices in Wales
- GP practices in Scotland
- GP practices in Northern Ireland
- Social care organisations
The assessment should cover potential exposure at all research sites, taking into account the North Wing, Russells Hall Hospital.

Further guidance is available in the guidance notes.

---

**A73-1. Will potential participants be identified through any organisations other than the research sites listed above?**

- [ ] Yes
- [x] No

---

**A74. What arrangements are in place for monitoring and auditing the conduct of the research?**

Monitoring and audit will be carried out in accordance with the usual practices of the DGH research and development directorate.

---

**A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?**

Guidance does not suggest that a DMC is required for this trial. Standard procedures for incident reporting will be followed, AEs recorded and any SAEs reported to the sponsor, in accordance with local guidance, as well as to the REC.

*If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.*

---

**A75-2. What are the criteria for electively stopping the trial or other research prematurely?**

We do not anticipate that this would be likely, since therapeutic procedures are as per usual practice. One criterion would be an unanticipated high rate of infection (three or more infections).

---

**A76. Insurance/ indemnity to meet potential legal liabilities**

*Note: in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland*

---

**A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? Please tick box(es) as applicable.**

*Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.*

- [x] NHS indemnity scheme will apply (NHS sponsors only)
- [ ] Other insurance or indemnity arrangements will apply (give details below)

*Please enclose a copy of relevant documents.*

---

**Total UK sites in study:**

1
A76-2. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? Please tick box(es) as applicable.

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

☑ NHS indemnity scheme will apply (protocol authors with NHS contracts only)
☐ Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
☐ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

☐ Yes ☐ No

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

☐ Yes ☐ No ☐ Not sure

PART B: Section 3 – Exposure to ionising radiation

Complete sub-sections A and/or B as applicable with input from relevant experts. It is advisable to discuss the proposed research at an early stage with (a) a Medical Physics Expert and (b) a Clinical Radiation Expert, who will carry out the required assessments for sub-sections C and D. The lead MPE can also facilitate the completion of sub-sections A and/or B if necessary.

1. Does the study involve exposure to radioactive materials?

☐ Yes ☐ No

2. Does the study involve other diagnostic or therapeutic ionising radiation?

☐ Yes ☐ No
A. Radioactive materials

Details of radioactive materials

B. Other ionising radiation

B1. Details of other ionising radiation

Give details by completing the table below:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No of procedures</th>
<th>Estimated procedure dose (use national Diagnostic Reference Levels where available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP, lateral and sky-line plain x-rays of the knee (if not performed already within last 6 months)</td>
<td>3 X-rays on one occasion</td>
<td>Total effective dose to standard subject estimated as 0.006 mSv for the set of 3 views.</td>
</tr>
</tbody>
</table>

C. Dose and risk assessment

C1. What is the total participant dose from all the exposures in A1 and/or B1, and what component of this is the additional dose over and above standard practice? What are the risks associated with these two doses (total and additional)?

The dose and risk assessment should be set out below. This should be prepared by a Medical Physics Expert (MPE) who is a registered clinical scientist registered with the Health Professions Council and has expertise relevant to the planned exposures. Where the study involves different types of exposure (for example, both radioactive materials and other ionising radiation, or more than one imaging method), advice may need to be sought from other MPEs with relevant expertise. The lead MPE should produce a combined assessment for the ethics committee, giving the names of any other MPEs who have contributed to the assessment. Further guidance is available by clicking on the information button or in the document “Approval of research involving ionising radiation”, available here: http://www.nres.npsa.nhs.uk/applications/guidance/research-guidance/#ion

For a standard patient the total effective dose from all 3 views is estimated as 0.006mSv, of which 0.002 mSv is from the third view not routinely performed.

0.006 mSv corresponds to approximately 1 day of background radiation in the uk. The excess risk of fatal cancer induction from a dose of 0.006mSv is estimated as 1 in 3 million to a healthy adult aged 40 in the uk, compared with a natural incidence of around 1 in 4. The excess risk of fatal cancer from the 0.02mSv for the extra view is around 1 in 10 million.

The medical and dental guidance notes denote radiation risks in research of this level as class I or trivial requiring minor societal benefit for justification.

A dose constraint may need to be set at locally for each participating site based on the maximum excess radiation compared with their standard practice.

Special attention must be paid to pregnant/potentially pregnant women or those who are breast feeding, or other potentially vulnerable groups.

C2. Declaration by lead Medical Physics Expert

I am satisfied that the information in sub-sections A and/or B and the assessment in sub-section C provide a reasonable estimate of the ionising radiation exposure planned in this research and the associated risks.

This section was signed electronically by Mr Mark Rawson on 11/09/2012 09:45.

Job Title/Post: Consultant Physicist

Organisation: Royal Wolverhampton Hospitals NHS Trust

Email: mark.rawson@nhs.net
C3. Details of person acting as lead Medical Physics Expert

<table>
<thead>
<tr>
<th>Title</th>
<th>Forename/Initials</th>
<th>Surname</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mr Mark</td>
<td>Rawson</td>
</tr>
</tbody>
</table>

Post: Consultant Physicist

Details of clinical scientist registration with the Health Professions Council:

Registration no: CSO1873

Organisation: Royal Wolverhampton Hospitals NHS Trust

Address: Dept of Medical Physics

The Deansley Centre, New Cross Hosp

Wolverhampton

Post Code: WV10 0QP

Telephone: 01902695522

Fax: 01902695652

Mobile: mark.rawson@nhs.net

D. Clinical assessment

This sub-section should be completed by a Clinical Radiation Expert (CRE) who is a registered doctor or dentist with clinical expertise relevant to the planned exposures. The assessment should cover potential exposure at all research sites, taking account of possible variation in normal clinical practice. Where the study involves different types of exposure (for example, both radiotherapy and other ionising radiation), advice may need to be sought from other CRES with relevant expertise. The lead CRE should produce a combined assessment for the ethics committee, giving the names of any other CRES who have contributed to the assessment. The guidance notes give advice to Chief Investigators on who can act as lead Clinical Radiation Expert (CRE) and advice for the CRE on the assessment of exposures having regard to IRMER.

Special attention must be paid to pregnant/potentially pregnant women or those who are breast feeding, or other potentially vulnerable groups.

D1. Will the exposure exceed the exposure that might be received as part of normal care at any proposed research site?

☐ Yes ☐ No

D2. Assessment of additional exposure

Explain how the planned exposure compares with normal practice and assess whether it is appropriate, using language comprehensible to a lay person. Consideration should be given to the specific objectives of the exposure, the characteristics of participants, the potential diagnostic or therapeutic benefits to the participant, the potential benefits to society, the risk to the participant and the availability of alternative techniques involving less, or no, ionising radiation.

If pregnant or breast-feeding mothers are to be studied give reasons and details of special radiation protection measures to be taken.

Third (skyline) view is now usually requested by orthopaedic surgeons in our organisation but less frequently by rheumatologists.

The use of this third view as routine is justified in the context of this study, as has been explained in previous sections.

D3. Declaration by lead Clinical Radiation Expert

I am satisfied that the exposure to ionising radiation planned in this research study (as defined in A1 and/or B1) is reasonable and that the risks are adequately described in the participant information sheet for the study.
Employers responsible for radiation facilities at research sites must have written procedures to meet the requirements of the Ionising Radiation (Medical Exposure) Regulations 2000 (IRMER). R & D offices for NHS sites will seek confirmation from local radiation experts that local IRMER authorisation procedures have been followed. Where the local Medical Physics Expert or IRMER Practitioner disagrees with the assessments made in this Section and/or the care organisation is unable to adhere to the protocol, this should be discussed with the Chief Investigator and the lead experts for the study. Any necessary variation in the protocol or participant information sheet at particular sites should be notified to the main REC as a substantial amendment and an ethical opinion sought.
### Part B: Section 5 – Use of newly obtained human tissue (or other human biological materials) for research purposes

#### 1. What types of human tissue or other biological material will be included in the study?
- Synovial fluid aspirated at the time of joint aspiration.
- Venous blood samples.
- Urine samples.

#### 2. Who will collect the samples?
- Initial blood and urine samples will be collected by the Research Fellow.
- Week 3 samples will be collected by the Biomedical Scientist as part of the week 3 review.
- Synovial fluid samples will be collected by the research fellow at the time of aspiration. Aspiration itself will be undertaken by a senior member of the rheumatology team.

#### 3. Who will the samples be removed from?
- [ ] Living donors
- [ ] The deceased

#### 4. Will informed consent be obtained from living donors for use of the samples? Please tick as appropriate

- In this research?
  - [ ] Yes
  - [ ] No

- In future research?
  - [ ] Yes
  - [ ] No
  - [ ] Not applicable

#### 5. Will any tissues or cells be used for human application or to carry out testing for human application in this research?
- [ ] Yes
- [ ] No

#### 6. Will the samples be stored: [Tick as appropriate]
- In fully anonymised form? (link to donor broken)
  - [ ] Yes
  - [ ] No

- In linked anonymised form? (linked to stored tissue but donor not identifiable to researchers)
  - [ ] Yes
  - [ ] No

  *If Yes, say who will have access to the code and personal information about the donor.*

- Identification number allocated at baseline assessment will be used to identify stored samples. Personal data linked to identification number will be stored in secure files in clinical research unit offices as described and will be available to the chief investigator.

- In a form in which the donor could be identifiable to researchers?
  - [ ] Yes
  - [ ] No

#### 7. What types of test or analysis will be carried out on the samples?
- 1. Serum high sensitivity CRP testing by ELISA
- 2. Serum IL6 (in Rheumatoid arthritis patients only)
This indicates the level of systemic inflammation.
3. Urine CTXII testing by ELISA
   This relates to the level of cartilage degradation occurring.
4. Synovial Fluid IL6 testing by ELISA.
   This relates to the level of inflammation within the joint.
5. Synovial fluid White cell count
   This relates to the level of inflammation within the joint.
6. Synovial fluid TNF alpha
   This relates to the level of inflammation within the joint.

No ethical issues are anticipated in connection with these tests, although very high CRP levels would warrant further investigation as a sign of pathology other than osteoarthritis but would not necessarily constitute reasons for withdrawal from the trial, since no further experimental procedure would be planned.

10. Will the research involve the analysis or use of human DNA in the samples?
    ○ Yes ☐ No

11. Is it possible that the research could produce findings of clinical significance for donors or their relatives?
    ○ Yes ☐ No

12. If so, will arrangements be made to notify the individuals concerned?
    ○ Yes ☐ No ☐ Not applicable

   If No, please justify. If Yes, say what arrangements will be made and give details of the support or counselling service.
   As detailed in section B9, unanticipated high CRP levels would warrant recall of the patient for clinical review, principally to ensure no evidence of infection is present. Under these circumstances, the patient will be contacted by telephone and reviewed on the Clinical Research Unit within 24 hours as necessary. No results would have immediate prognostic or predictive significance for either patients or relatives beyond this possibility.

13. Give details of where the samples will be stored, who will have access and the custodial arrangements.

   Samples will be stored within the laboratory facilities at the Clinical Research Unit. This area is under the supervision of Jackie Smith, Chief Biomedical Research Scientist. Access will be restricted to Jackie Smith and Sue Cadman, Biomedical Scientist. The laboratory is located within the Clinical Research Unit and entry to the laboratory facilities requires an electronic security pass. The entire unit is locked electronically between the hours of 1700 and 0830 and is not accessible.

14. What will happen to the samples at the end of the research? Please tick all that apply and give further details.

   [ ] Transfer to research tissue bank

   (If the bank is in England, Wales or Northern Ireland the institution will require a licence from the Human Tissue Authority to store relevant material for possible further research.)

   [ ] Storage by research team pending ethical approval for use in another project

   (Unless the researcher’s institution holds a storage licence from the Human Tissue Authority, or the tissue is stored in Scotland, or it is not relevant material, a further application for ethical review should be submitted before the end of this project.)

   [ ] Storage by research team as part of a new research tissue bank

   (The institution will require a licence from the Human Tissue Authority if the bank will be storing relevant material in England, Wales or Northern Ireland. A separate application for ethical review of the tissue bank may also be
Please give further details of the proposed arrangements:

Samples will be stored at -80 degrees centigrade within the laboratory until analysed. It may be desirable to test samples for further factors as yet identified, subject to our initial results. For this to occur, a further application to the REC would be required.
PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.

<table>
<thead>
<tr>
<th>Research site</th>
<th>Investigator/ Collaborator/ Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institution name</td>
<td>Dr</td>
</tr>
<tr>
<td>Department name</td>
<td>First name/ Initials</td>
</tr>
<tr>
<td>Street address</td>
<td>Surname</td>
</tr>
<tr>
<td>Town/city</td>
<td>Hirsch</td>
</tr>
<tr>
<td>Post Code</td>
<td>George</td>
</tr>
</tbody>
</table>

| | |
| Russells Hall Hospital | |
| Clinical Research Unit | |
| Dudley, West Midlands | |
| DY1 2HQ | |
D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.

9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

   - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
   - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
   - May be seen by auditors appointed to undertake accreditation of REC's (where applicable).
   - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

11. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee’s final opinion or the withdrawal of the application.

**Contact point for publication** (Not applicable for R&D Forms)

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- [ ] Chief Investigator
- [ ] Sponsor
Study co-ordinator  
Student  
Other – please give details  
None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – *please tick as appropriate:*

☐ I would be content for members of other REC’s to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by dr george hirsch on 10/09/2012 10:45.

Job Title/Post: Research Fellow
Organisation: Dudley Group NHS FT  
Email: gandnhirsch@tiscali.co.uk
Signature: ....................................................
Print Name: George Hirsch
Date: 10/09/2012 *(dd/mm/yyyy)*
D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.

7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

This section was signed electronically by Margaret Marriott on 10/09/2012 11:58.

Job Title/Post: R&D Manager
Organisation: DGH
Email: margaret.marriott@dgh.nhs.uk
D3. Declaration for student projects by academic supervisor(s)

1. I have read and approved both the research proposal and this application. I am satisfied that the scientific content of the research is satisfactory for an educational qualification at this level.

2. I undertake to fulfil the responsibilities of the supervisor for this study as set out in the Research Governance Framework for Health and Social Care.

3. I take responsibility for ensuring that this study is conducted in accordance with the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research, in conjunction with clinical supervisors as appropriate.

4. I take responsibility for ensuring that the applicant is up to date and complies with the requirements of the law and relevant guidelines relating to security and confidentiality of patient and other personal data, in conjunction with clinical supervisors as appropriate.

Academic supervisor 1

This section was signed electronically by Rainer Klocke on 10/09/2012 18:06.

Job Title/Post: Consultant Rheumatologist
Organisation: Dudley group for health NHS FT
Email: Rainer.Klocke@dgoh.nhs.uk
29 October 2012

Dr George Hirsch
Research Fellow in Rheumatology
Dudley Group NHS Foundation Trust
Clinical Research Unit, 1st floor,
North Wing, Russells Hall Hospital
Dudley
DY1 2HQ

Dear Dr Hirsch

Study title: An investigation of psychological and other predictors of pain reduction to open-label corticosteroid injection in primary and secondary osteoarthritis of the knee.

REC reference: 12/YH/0457

Thank you for your letter of 19 October 2012, responding to the Committee’s request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.
Management permission or approval must be obtained from each host organisation prior to
the start of the study at the site concerned.

*Management permission (“R&D approval”) should be sought from all NHS organisations
involved in the study in accordance with NHS research governance arrangements.*

Guidance on applying for NHS permission for research is available in the Integrated
Research Application System or at [http://www.rdforum.nhs.uk](http://www.rdforum.nhs.uk).

*Where a NHS organisation’s role in the study is limited to identifying and referring potential
participants to research sites ("participant identification centre"), guidance should be sought
from the R&D office on the information it requires to give permission for this activity.*

*For non-NHS sites, site management permission should be obtained in accordance with the
procedures of the relevant host organisation.*

*Sponsors are not required to notify the Committee of approvals from host organisations*

**It is the responsibility of the sponsor to ensure that all the conditions are complied
with before the start of the study or its initiation at a particular site (as applicable).**

**Approved documents**

The final list of documents reviewed and approved by the Committee is as follows:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
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<tbody>
<tr>
<td>Covering Letter</td>
<td></td>
<td>12 September 2012</td>
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<tr>
<td>GP/Consultant Information Sheets</td>
<td>1</td>
<td>27 March 2012</td>
</tr>
<tr>
<td>Investigator CV</td>
<td></td>
<td>12 September 2012</td>
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<tr>
<td>Other: Academic Supervisor CV: Rainer Klocke</td>
<td></td>
<td>11 September 2012</td>
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<tr>
<td>Other: Letter from statistician</td>
<td></td>
<td>09 August 2012</td>
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<tr>
<td>Other: Reply slip</td>
<td>1</td>
<td>27 March 2012</td>
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<tr>
<td>Participant Consent Form</td>
<td>3</td>
<td>18 October 2012</td>
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<tr>
<td>Participant Information Sheet</td>
<td>3</td>
<td>18 October 2012</td>
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<tr>
<td>Protocol</td>
<td>2</td>
<td>08 August 2012</td>
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<tr>
<td>Questionnaire: Womac Osteoarthritis Index VA 3.1</td>
<td>3</td>
<td></td>
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<tr>
<td>Questionnaire: Illness Perception Questionnaire for Knee Osteoarthritis</td>
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<td>Questionnaire: Goals for Arthritis Treatment Questionnaire</td>
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<td>Questionnaire: Health Care Climate Questionnaire in the Context of Arthritis Treatment</td>
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<td>Questionnaire: Medication Questionnaire</td>
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<tr>
<td>Questionnaire: PCS Questionnaire</td>
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<tr>
<td>Questionnaire: Arthritis Treatment Self Regulation Questionnaire</td>
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<td>Questionnaire: Vitality Scale</td>
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<td>Questionnaire: AIMS Questionnaire</td>
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<tr>
<td>REC application</td>
<td></td>
<td>10 September 2012</td>
</tr>
<tr>
<td>Response to Request for Further Information</td>
<td></td>
<td>19 October 2012</td>
</tr>
</tbody>
</table>

**Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for
Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

**After ethical review**

**Reporting requirements**

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

**Feedback**

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

| 12/YH/0457 | Please quote this number on all correspondence |

With the Committee’s best wishes for the success of this project

Yours sincerely

Pp Dr Basil Sharrack
Chair

Email: nrescommittee.yorkandhumber-sheffield@nhs.net

**Enclosures:** “After ethical review – guidance for researchers” [SL-AR2]

**Copy to:** Mrs Margaret Marriott, Dudley Group NHS Foundation Trust