Assessing the effect of IFT and exercise therapy on OA knee.

Dyson, Craig

Assessing the Effect of IFT and Exercise Therapy on OA Knee

Craig Dyson
BSc(HONS) Physiotherapy

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Summary

Background:
Osteoarthritis (OA) is a chronic, degenerative disease that mainly affects weight bearing joints and is the most common disease of the musculoskeletal system (Naredo et al, 2005). It is estimated to affect It is thought that as many as 10% of people over the age of 65 in the US suffer with the disease (Felson, 1982) leading to an economical cost of around $86 billion (Abell 2005). Therefore the best ways to manage the condition are important to keep the physical functioning of the individual sufferer high and the cost to the economy low.

Aims:
The aim of this MPhil thesis is to explore and present the current research surrounding the use of exercise therapy and Interferential Therapy (IFT) in the use of Osteo-arthritis (OA) of the knee. The thesis also aims to test whether the combination of the two treatment methods is more effective than either treatment used in isolation.

Methods:
The current research on the use of IFT and exercise therapy will be presented as a review of the defined area. The clinical assessment of the treatment modalities will be tested in a pilot study that is presented as a single-blind randomised controlled trial.

Results:
The review chapter of the study reports that there is a perceived benefit of exercise therapy and IFT in the treatment of OA knee. However, the types of exercise and frequency needed have yet to be clarified. The use of IFT in the treatment of OA knee has yet to be researched in any great depth, although previous studies do suggest that it may have a beneficial effect even though the optimum settings have yet to be clarified.
In the study presented it was found that exercise therapy produced the best results when compared with IFT in isolation. However, the combination of IFT and exercise therapy did also produce significant improvements.

Conclusion:
The thesis highlights the need for further research into the areas of IFT and exercise therapy as treatments for knee OA. The lack of uniformity in both areas of research makes comparison of treatment methods difficult, and as a result it is difficult to draw any definite conclusions, although exercise therapy does appear to be successful in the treatment of knee OA. The pilot study as part of the thesis demonstrates that the methodology used is a robust and innovative way of assessing the effect of IFT and exercise therapy in the clinical environment, and could be used as part of a larger scale multi-centre trial. The results of the study chapter appeared to demonstrate that the combination of treatments outlined above was the most effective in the treatment of knee OA. Further studies are needed to assess whether any further improvements of the combination treatments are cost-effective.

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To my loving wife, Kirsten. I now have something to show for the months of stress that I have caused you.

Contents

List of Abbreviations

OA.....**Osteoarthritis**
ACR.....**American College of Rheumatology**
UK.....**United Kingdom**
US.....**United States**
ml.....**millilitres**
mg.....**milligrams**
ROM.....**Range of motion**
IASP.....**International association for study of pain**
IFT.....**Interferential Therapy**
T-Cell.....**Transmission Cell**
DNA.....**De-oxyribonucleic acid**
PGM.....**Periaqueductal grey matter**
RVM.....**Rostal ventral matter**
NRM.....**Nucleus raphe magnus**
STT.....**Spinothalamic tract**
NSAID.....**Non-steroidal anti-inflammatory drugs**
RCT.....**Randomised controlled trial**
Hz.....**Hertz**
TENS.....**Transcutaneous electrical nerve stimulation**
ms.....**microsecond**
mmHg.....**millimetres Mercury**
SETT.....**Sub-maximal effort tourniquet test**
VAS.....**Visual analogue scale**
LBP.....**Low back pain**
MT.....**Manual/manipulative therapy**
BSR.....**Blood sedimentation rate**
CRP.....**C-reactive protein**
MRI.....**Magnetic resonance imaging**
ACL.....**Anterior cruciate ligament**
BMI.....**Body mass index**
WOMAC.....**Western Ontario and Mcmaster universities index**
Vs.....**Versus**
RM.....**repetition maximum**
GP.....**General practitioner**
n.....**number of subjects**
HADS.....**Hospital anxiety and depression score**
mins.....**minutes**
secs.....**seconds**
hr.....**hour**
i.e.....***id est*- that is**
etc.....***et cetera*- and other things**
NRS.....**Numerical rating scale**
lbs.....**pounds**

1.0 Thesis Introduction

1.1 Introduction

Osteoarthritis (OA) is a chronic, degenerative disease that mainly affects weight bearing joints and is the most common disease of the musculoskeletal system (Naredo et al, 2005). It has been defined by the American College of Rheumatology (ACR) to be "a heterogeneous group of conditions that lead to joint signs and symptoms, which are associated with defective integrity of articular cartilage."(Sarzi-Puttini 2005). Several authors have previously highlighted the common view that OA most commonly affects the joints of the lower limb, in particular the hip and the knee, with the knee being the most commonly affected (Felson 1987; Mcalindon 1992; Sisto 2006). Furthermore, Peat et al. (2001) stated that OA affecting the knee is the most common form of arthritis and a major contributor to functional impairment and reduced independence in older adults.

1.2 Rationale

An estimated 7-11% of the populations of developed countries have symptomatic OA, and around 27-44% of that figure, have been diagnosed with radiographic disease (Naredo 2005). In particular, Rat et al.(2004) reported that the annual incidence of radiographically diagnosed OA in the UK is expected to be around 3.1%, compared to the annual European incidence of knee replacement surgery being 0.5-0.7 per 1000 (Dieppe 1999) . In the US in 2001, an estimated 70 million Americans reported having arthritis or chronic joint symptoms, with an expected 59.4 million expected to suffer from OA alone by 2020, and in 1997 arthritis cost the US an estimated $86 billion (Abell et al, 2005). Globally, the disease is expected to become the fourth most important cause of disability amongst women, and the eighth most important among men (Murray 1997).

Due to the nature of the disease, the prevalence increases with age, and with the average age of the population also set to rise (by 2040, the number of people over 65 in the US will account for almost 25% of the population (Hamerman 1995)), the incidence of OA is likely to increase. With the number of people living with OA of the knee increasing, combined with increasing health costs, it is important to find the most appropriate and cost effective way to manage the condition if society is to maintain a healthy population.

1.3 Aims and Objectives

The aim of the presented thesis is to describe the evaluation of currently used treatment techniques in OA of the knee. The current chapter aims to describe pathological changes that occur in a joint affected by OA with a further description of the pain mechanisms related to the stage of the disease. The thesis then aims to present possible methods of treatment of OA of the knee with review of the current literature on the described treatment techniques. The evaluation of the chosen treatment will then be presented with a randomised single blind controlled pilot study with conclusion of the overall process.

1.4 Pathogenesis of OA of the Knee

1.4.1 Causal Factors

Traditionally, OA has been thought to be due to natural 'wear and tear' of the joints. However, recent research suggests that this view may be too limited (Andriacchi 2004). More current thoughts suggest that the disease is a result of multiple causes including local and systemic mechanisms, with various mechanical, biochemical and genetic factors contributing to pathologic changes around the joint (Sarzi-Puttini 2005; Goldring 2007; Rubin 2008; Underwood 2009).
The following theories are postulated to be possible contributing factors towards osteoarthritis:

1. **Increased load through the joint**: Abnormal load through the joint has been attributed as the main cause of joint incongruity. When the load is excessive, chondrocyte death is thought to lead to articular cartilage damage (Rubin 2008).
2. **Stiffness of subchondral bone:** If subchondral bone has an increased stiffness, the articular cartilage of a joint is forced to cope with an increased load due to the subchondral bones inability to dissipate force (Rubin 2008).
3. **Biochemical abnormalities**: Reduced proteoglycan content leads to water binding increasingly to collagen in the joint. This increases swelling of fibrillated cartilage. More enzymes have been found in osteoarthritic cartilage than in normal cartilage. Collagenase is found in increased quantity along with Acid cathepsin, which attacks the essential constituent collagen and the protein cores of the matrix macromolecules (Rubin 2008).
4. **Genetics**: Studies of identical twins have shown an increased genetic disposition towards osteoarthritis. It is thought to be due to a mutation in the gene for type II collagen (Rubin 2008).

1.4.2 Structural Consequences

As outlined previously, the disease processes cause structural changes that specifically affect the articular cartilage, subchondral bone and synovial membranes, whereby the cartilage can become degraded, the bone hypertrophied and thickened whilst the synovial membranes become inflamed (Pelletier et al., 1998 in Groer, 2001).

This process can be broken into three stages:

- Stage I details the breakdown of the cartilage matrix.

Initially, loss of proteoglycans in the surface articular cartilage and death of chondrocytes (chondrocytes are the only cells found in cartilage) can be detected. As a result, any viable chondrocytes enlarge and aggregate into groups. The disease process can remain at this

stage for many years before further progression leads to breakdown (fibrillation) of the normally smooth surface cartilage (Rubin 2008; Underwood 2009).

- Stage II involves the erosion of the cartilage surface with breakdown products being released into the synovial fluid of the joint.

The fibrillation continues, leading to synovial fluid penetrating the cracks in the cartilage, almost like a weathering process. This process leads to the cracking of the cartilage which leads to pieces of articular cartilage in the synovium of the joint. Further cracking of the cartilage can lead to the subchondral bone extending into the cracks inducing subchondral osteoclastic bone resorption. It is possible that symptoms are felt at this stage of the disease (Martel-Pelletier 2004).

- Stage III results in synovial inflammation and release of various chemicals which lead to further collagen degradation (Martel-Pelletier, 2004).

Inflammation in the joint is thought to occur as a result of articular cartilage lodging in the synovium. During disease progression, the subchondral bone can extend into the joint surface at irregular intervals- this leads to the development of subchondral cysts in the bone marrow. Osteophytes (bony spurs) can also develop, usually in the lateral portions of the joint causing further irregularity of the joint surface and the characteristic signs on X-ray (Rubin 2008).

1.4.3 Clinical Presentation

Signs and symptoms of the above structural changes can vary in timescale and patient, although as the disease progresses the involved joint can be expected to exhibit any of the following:

1. Joint pain which is present on movement. Pain can be caused by inflammatory irritants within the joint, and by the stretching of contractures in the later stages of the disease.(Rubin 2008).
2. Stiffness within the joint which is mainly present during inactivity. This is thought to be due to the inflammatory process ongoing in the affected joint (Underwood 2009).
3. Audible creaking of the joints (crepitus).

4. Decreased muscle strength in the main muscles surrounding the joint. As a result of decreased movement, surrounding musculature often atrophies leading to increased weakness (Underwood 2009).
5. Reduction in joint range of movement. This can be the result of joint or muscle contractures, large osteophytes or joint incongruity. This is often a sign of disease progression (Alkhazim 2004; Rubin 2008).

In various stages of OA the presenting symptoms are often reported as being pain, inflammation and swelling (Felson 2006). It is postulated that with the swelling that occurs, quadriceps muscle inhibition can follow when as little as 1ml of fluid accumulates in the knee (DeAndrade 1965). This is not the only mechanism that can lead to quadriceps inhibition, as Hurley and Newham (1993) suggest that abnormal afferent (towards the brain) information from the damaged joint can also have a similar affect. The quadriceps muscle group is important, as it has been shown that with decreased quadriceps function there is a likelihood that there would be decreased postural stability confidence and impaired performance on activities of daily living (Hurley 1998). The pain that accompanies the quadriceps inhibition can lead to disuse atrophy, which will have a further weakening effect on the surrounding musculature (Vad 2002). These effects of OA can, if allowed to continue, lead to decreased function and therefore it is essential to try and arrest the damaging effects of OA at an early a stage as possible. Exercise therapy can be used as it has been shown to increase quadriceps strength (Maurer 1999; Foley 2003; Huang 2005; Mikesky 2006; Iwamoto 2007), and has further been shown to decrease pain (Maurer 1999; Fransen 2001; Cheing 2002; Evcik 2002; Fitzgerald 2002; Huang 2003; Bennell 2004; Eyigor 2004; Ravaud 2004; Huang 2005).

If OA is allowed to progress, a subsequent symptom is reduced range of motion (ROM). This occurs due to a number of factors including muscle spasm, muscle contracture, capsular contracture, joint surface incongruity and mechanical block due to osteophytes or loose bodies (Rubin 2008). The three aforementioned effects often occur earlier in the disease process and can possibly be addressed through exercise. Vad et al. (2002) state that

adequate flexibility and elasticity of the periarticular soft tissues and musculature is essential in permitting proper ROM as well as protecting the joint from undue stress.

It is usually at this stage of the disease process that the effect on patient function becomes apparent. As the disease progresses, patients often complain of increased pain whilst weightbearing, and reduced walking distances and stair-climbing ability (Sarzi-Puttini 2005).

1.5 Pain Mechanisms

Pain is defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (IASP 1994).
The initial part of the pain nociceptive chain is believed to be the nociceptor (a pain receptor that can respond to noxious mechanical and thermal stimuli) which is composed of a number of chemical and sensory receptors which leads to the polymodal nature of nociceptive neurons (Besson 1987; Millan 1999). Chemical substances which are released following actual or potential tissue trauma include Bradykinin, Substance P and Prostaglandins. These substances secreted at noxious levels interact with nociceptors leading to the generation of a receptor potential, which is the initiation of the action potential that will be propagated along the peripheral nerve and then enter the central nervous system via the spinothalamic or spinoreticular pathways (Walsh 1997). Activation of these pathways leads to the nociceptive nerve impulse arriving at the central nervous system, where interpretation of the pain occurs at the brainstem, thalamic and cortical level. It is this interpretation process that leads to the psychological and behavioural response to the damage that has occurred (Almeida 2004).

The afferent fibres described previously can be split into two main types that transmit nociceptive impulses. The two types are A-delta and C-fibres (Snell 2010). The A-delta fibres are myelinated and fast conducting, with the C-fibres being the non-myelinated, slow conducting fibres (Mountcastle 1980; Kitahata 1993). The fibres terminate in Laminae I and V of the dorsal horn of the spinal cord (Millan 1999). In the presence of more chronic,

inflammatory noxious stimulus, such as OA, these fibres can become sensitized and start to discharge spontaneously which may give rise to the throbbing pain or soreness experienced following injury (Bennett 2000; Almeida 2004). When noxious impulses reach the spinal cord from the periphery, it reaches the first possible site of modulation, which could be a site manipulated by IFT through the pain gate mechanism as described by Melzack and Wall (1965) (De Domenico 1982).

1.5.1 Pain Gate Theory

Melzack and Wall (1965) initially conceptualized the idea that pain modulation may be achieved via various treatment options, and it has been widely cited as the mechanism of action responsible for electrotherapy induced hypoalgesia (Johnson 1999). The postulated Gate Control theory outlines the importance of stimulating the small diameter C fibres. This theory proposes that there is a mechanism by which stimulation of one set of fibres will override or close the 'gate' to another set of fibres. Evidence suggests this 'gate' is located in the cells of the substantia gelatinosa, which lie in the dorsal horn of the spinal cord (specifically laminae II)(Melzack 1965). It states that the cells in the substantia gelatinosa act as a gate control system that modulates the afferent pain stimulus before they influence the transmission cell (T-Cell). The T-Cell can then activate neural mechanisms which compromise the action system responsible for response and pain perception (Melzack 1965). This system can be affected at the dorsal horn level by brain processes concerned with previous pain experiences. The theory further suggests that stimulation of large diameter fibres following a painful response will dampen down the small diameter fibres that will be most active following a painful stimulus. In summary, it is proposed that the presence or absence of pain is determined by the balance between the sensory and central inputs to the gate control system.

With regards to electrotherapeutic modalities, such as IFT, it is thought that they produce their pain relief via the selective activation of the large diameter afferent fibres (De Domenico 1982). DeDomenico (1982, 1987) suggested that a treatment frequency of approximately 100Hz may be successful in closing the pain gate, thus producing analgesia.

In contrast, other authors (Johnson 1999; Palmer 1999) have questioned whether this 100Hz frequency is effective via this mechanism, whilst it has further been suggested that it is difficult to determine whether or not the frequency created deep in the tissues (beat frequency) or the carrier frequency is responsible for the selective activation of the large diameter nerve fibres. However regardless of mechanism of action, Goats (1990) reports that IFT induced analgesia can be created within clinical practice at these frequencies (Goats 1990). There remains several unanswered questions as to how this theory, even though accepted, can be supported by existing neurophysiological evidence.

1.5.2 Descending Pain Inhibition

In addition to the Gate Control Theory, another postulated mechanism of action for effective pain relief is that of the Descending Pain Suppression Pathway. This theory documents the important role that 'biological painkillers' such as endorphins, dynorphins and enkephalins (collectively known as endogenous opioids) have on modulating pain in the human body (Basbaum 1978). These opioids have similar pharmacological characteristics as morphine and are said to have an important role in the transmission of nociceptive impulses from primary afferent nerves (Stamford 1995; Fields 1999).

Recombinant DNA technology has detected that these compounds have specific receptor sites and that they are intimately involved in the descending pain suppression system (Stamford 1995).

The main areas of this system are:

1. Periaqueductal Grey Matter (PAG), as this area is an area rich in opioid receptors.
2. Rostal Ventral Medulla (RVM), as this comprises the Nucleus Raphe Magnus (NRM) and reticular nuclei.
3. The Spinal Dorsal Horn.

The descending pain pathway is based upon the principle that a nociceptive impulse travels via the spinoreticular and spinothalamic tracts in the spinal cord to the thalamus in the brain, and these pathways have collateral neurological communication with the PAG, NRM and RVM. As a consequence, this causes endogenous opioid release at the PAG and NRM,

which descend via projection neurones to the spinal dorsal horn, resulting in the inhibition of pain transmission (Basbaum 1978).

Stamford (1995) documented that stimulation of the PAG has been shown to reduce the activity of cells in the Spinothalamic Tract (STT) (which transmits nociceptive impulses) in monkeys, thus reducing pain. Furthermore, activation of the PAG has been shown to inhibit cells of the nociceptive responses of dorsal horn neurons (Stamford 1995). The PAG has connections to the NRM (Hudson 1996). The NRM, which is important in pain modulation, is thought to modulate some of the effects of PAG stimulation (Stamford 1995). The NRM, not only modifies the effects of neighbouring groups of cells, but also has its own effects on pain, as direct stimulation of this area has been shown to cause analgesia in behavioural algeriometric tests (Oliveras 1975) from (Stamford 1995), and has been shown to decrease the response of dorsal horn cells to noxious heat (Llewelyn 1986) from (Stamford 1995). De Domenico (1982) states that stimulation of the smaller diameter fibres is important if IFT is to have an effect via this pain mechanism. To achieve this, a pulse frequency of approximately 15Hz with a pulse width of approximately 100-200 microseconds is needed even though this pulse width is likely to stimulate larger diameter fibres. The method via which IFT has an effect on this system remains unclear. Some authors postulate that it may be due to the pulse duration which can be altered to between 100-200μs with a low frequency, thus stimulating all types of nerve fibre, and favouring the activation of the descending pain suppression mechanism (Howson 1978); cited De Domenico (1982).

1.5.3 Physiological Pain Block

This theory states that neurones have a maximum rate at which they can transmit action potentials. If the axon of the nerve is stimulated at a rate greater than it is able to transmit, the axon will eventually cease conducting (Goats 1990). DeDomenico (1987) proposed that A-delta fibres will be unable to transmit nociceptive impulses if a frequency of greater than 40Hz is applied. Other sources also suggest that 40Hz would lead to the larger neurons ceasing transmission (Brown 1985).

Therefore, a stimulus of 100Hz should cause a 'physiological block' leading to an analgesic effect. This effect is accepted by other authors (Brown 1985; DeDomenico 1987; Goats 1990) however, it has yet to be proven by using IFT currents.

1.5.4 Placebo Effect

The Placebo Effect is a less understood mechanism that any therapist has to consider may be playing a part during any treatment procedure Richardson (1994) states that a certain effect of any treatment procedure could be due, in part, to the placebo phenomenon. In the generation and application of IFT, there is a high level of technology involved and the units are often visually impressive (Johnson 1999). This is one of various stimuli that could lead the patient to believe that they must be receiving an effective treatment. DeDomenico (1987) states that an IFT unit is impressive, and in some cases, bewildering for the patient and this, combined with the array of flashing lights is likely to induce a certain amount of awe in the patient, thus leading to the feeling that the patient must be receiving an effective treatment. The therapist-patient relationship can also play a part as (Richardson 1994) Richardson (1994) suggests what he calls a 'Cognitive Dissonance Theory' where the patient holds two beliefs that are psychologically inconsistent- a dissonance. The patient tries to resolve this by altering their perception of their symptoms and trying to please the treating therapist.

1.6 Current Treatment of Knee OA

Current treatment strategies for the effective management of people with osteoarthritis involve pharmacological, non-pharmacological or surgical approaches (Jordan 2003). With regards to the pharmacological treatment options, the most common agents currently recommended include Paracetamol, Non-steroidal anti-inflammatory drugs (NSAIDS), Steroids (Oral or Topical), or opioid analgesics (Jordan 2003). Non-pharmacological interventions include different types of exercise (strengthening, aerobic, hydrotherapy), patient education, self-management, heat/ice, acupuncture, ultrasound and weight loss.

Common surgical techniques used include joint lavage, arthroscopic debridement and total joint replacement (Jordan 2003).
Due to the large costs involved and the rising average age of the population, surgical techniques are often seen as the last resort, therefore other types of treatments are often sought to achieve cost effectiveness and maintenance of function (Sevick 1999). Whilst pharmacological treatments have been shown to be effective (Zhang et al., 2007), NSAIDS have been reported to have possible adverse effects on cartilage metabolism, and can lead to bowel irritation and stomach ulcers (Brandt 1987; Bradley 1991).
The most commonly researched area of non-pharmacological treatment is exercise therapy (Zhang et al., 2007) and this is the area that will be further explored.

1.6.1 Exercise Therapy

Physiotherapy is one form of non-pharmacological treatment that can be used to treat knee OA and one of the forms of physiotherapeutic treatment applied is exercise therapy (Jamtvedt 2008). Exercise therapy can be used to address many of the adverse clinical effects outlined previously (Maurer 1999; Bennell 2004).

Previous research studies have indicated the therapeutic potential that an exercise based intervention could have upon a person's physical function and mobility (Rejeski 1998; Maurer 1999; Deyle 2000; Fransen 2001; Fitzgerald 2002; Foley 2003; Huang 2003; Bennell 2004; Eyigor 2004; Deyle 2005; Roos 2005; Karatosun 2006). It is essential that OA is controlled as early as possible in its process because if joint surface incongruity and mechanical block of the joint has occurred the patient is often unlikely to respond to exercise, making surgery the most probable course of action. Therefore, if non-invasive techniques (such as exercise therapy) are to be successful in the effective management of people with OA of the knee, it is important that these interventions are implemented as early as possible in the disease process.

Cheing (2002 and 2004) reports that existing research carried out on the effects of exercise therapy has proven to be overall very positive, however the types of exercises that have been researched vary, and often require the use of expensive machinery, such as the Kin-

Kom machines which measure kinematics around a joint. Due to the level of potential financial resources of hospital departments, the clinical implementation of this approach would be hindered.

Previously published studies have examined the effects of exercise therapy on knee OA, and these will be explored in more depth in the systematic review chapter of this thesis. Van Baar (1999) carried out a systematic review of the Randomised Clinical Trials (RCT) that examined the effects of exercise therapy on pain, self-reported disability, and patients assessment of effect in patients with knee and hip OA. Eleven RCTs met the inclusion criteria for the systematic review and the author concluded that exercise therapy was effective in the treatment of the parameters outlined. However, due to the limited numbers of studies that met the criteria it was also recommended that more studies of high methodological quality be carried out.

Fransen et al. (2001) carried out a systematic review to determine whether exercise is beneficial in terms of joint pain, physical function and patients' assessment of effectiveness for people with OA of the knee. Seventeen studies compared a form of land based exercise with a non-exercise group. The results of the review indicate that land based exercise was found to be beneficial in terms of self-reported pain and self-reported function. However, although it is agreed that quadriceps strengthening needs to be one of the main considerations, the types of exercises, frequency of exercises, exercise settings and delivery of exercises outlined in the studies varied widely and therefore one of the authors' conclusions was that further investigation needed to be carried out on optimal exercise type and dosage.

In 2004 a group of twenty experts in the field of OA were gathered to offer opinions on type of exercise to be used in conjunction with knee OA (Roddy 2005). Each expert offered ten key points on exercise and each of these key points were scored according to the Delphi technique until eventually ten key points were determined. Included in these key points were:

1. Exercises needed to be a mix of aerobic and strengthening exercise.

2. Improvements in muscle strength and proprioception gained from exercise programmes may reduce the progression of knee and hip OA.
3. There are few contraindications to the prescription of strengthening or aerobic exercise in patients with hip or knee OA.

1.6.2 Interferential Therapy

Although exercise has been shown to be effective in reducing pain (Fransen 2001), many patients find that during an acute phase, exercise can increase pain or the thought of exercise can be off-putting (Thorstensson 2006), and therefore therapists often look to other modalities to have an effect on pain. One other commonly used technique (Lindsay 1990; Pope 1995) is Interferential Therapy (IFT).

IFT is a non-invasive electrotherapy technique that can be used for both muscle stimulation and pain relief (Noble 2006). In the context of this study it shall be reviewed in terms of its pain relieving effect.

1.6.2.1 Generation of interferential therapy currents

IFT is a non-invasive electrotherapeutic modality that uses electrical stimulation through adhesive pads, suction pads or sponge pads to stimulate nerves and achieve a variety of different effects (Noble 2000). Reported effects include pain relief (Stephenson 1995; Werners 1999; Johnson 2003), reduction of swelling (Jarit 2003), healing of wounds and fractures (Savage 1992) and restoration of function (Mantle 1991; Savage 1992; Jarit 2003).

An IFT unit is said to produce a low frequency pulse termed a 'beat frequency' which generates a nerve impulse (Noble 2000). The beat frequency is usually set by the IFT unit but is often able to be modified by the user at between 1 and 250Hz, which enables a strong effect at a deeper surface, i.e. within the joint, without irritating the area of skin surface that it is applied to (Goats 1990). The same low frequency applied by other modalities, such as

Transcutaneous Electrical Nerve Stimulation (TENS) would lead to considerable discomfort at the skin surface due to the impedance of the skin, which provides high electrical resistance. The low frequency treatment of IFT is enabled through the use of alternating medium level currents which meet little resistance when penetrating the skin surface (Goats 1990). The frequency can be targeted at a certain area which is often within a joint, through the use of two medium frequency currents which 'interfere' with each other at a depth determined by the operator of the IFT (please refer to figure 1) (De Domenico 1987; Kloth 1987; Noble 2000; Watson 2008).

The interference that is created in the underlying tissue is termed the 'beat frequency', and, as was explained earlier, imitates a low frequency current. In bipolar machines (a machine that employs 2 contact electrodes), the beat frequency is created by the Interferential unit, in quadrapolar machines (a machine that employs 4 contact electrodes) the beat frequency can be generated within the target tissue, depending on the type of machine. The beat frequency is created through the 'interference' of one constant 'carrier' frequency with another frequency generated by a second circuit (Robertson 2006), and is equal to the difference in frequency of the two generated currents (i.e. 4000Hz and 4100Hz results in a 100Hz beat frequency) (Goats 1990).

It is the decision of the operator which frequency to apply as different frequencies will lead to differing treatment effects (De Domenico 1981).
Another variable that can be adjusted with IFT units is the mode of the beat frequency. It can usually be set at a constant or rhythmical mode. This refers to whether, or not the 'beat frequency' will change as it is applied to the tissue. In the constant mode, the unit will deliver a constant beat frequency, usually set at 1-250Hz. In the rhythmical setting, the therapist is able to select values that the machine will continuously reflect between. The time taken for the unit to 'sweep' between the selected frequencies (e.g. 10-100Hz) can often also be selected (e.g. 6/6, meaning that the machine takes 6 seconds to reach the highest selected frequency and 6 seconds to reach the lowest selected frequency). A possible reason for applying the sweep is that nerves become accustomed to a constant frequency (De Domenico 1982), and therefore, by applying the sweep, the frequency can

change continually reportedly making the IFT more effective for a more prolonged period (DeDomenico 1987). It has been postulated that use of a smaller frequency range will tend to be a more efficient use of IFT Quirk (1985). There are different types of sweep settings that can be used according to the desired physiological effect. The different types of sweep pattern will not be explored in detail in this review. However, the main types of sweep pattern are the triangular, rectangular and the trapezoidal sweep patterns. A common setting for IFT might be 80-120Hz, employing a 6^6 triangular sweep for 25minutes. This means that the 'beat frequency' will change from 80-120Hz over a period of six seconds, and will continue to do so for twenty-five minutes (for a list of variables that can be adjusted with IFT, please see Table 1).

Table 1: Summary table to highlight IFT variables

Treatment Parameter/Method of Application	Example of Variable Choice	Description
Beat Frequency/Amplitude Modulated Frequency	Can usually be alternated between 1-250Hz	This component of IFT is traditionally considered to be the most important as it is thought to be the key factor in nerve stimulation.
Frequency Sweep	6^6, 1^1	This describes the transition from one beat frequency to another.
Electrode Application Placement	Four Electrode, Two Electrode	Four electrode placement is considered to produce a 'clover leaf pattern' of current, whereas two electrode placement mixes the two currents in the stimulator prior to delivery.
Electrode Application Method	Suction or Plate electrodes	Electrodes can be placed using a suction unit which adheres to the skin or using carbon rubber electrodes in damp sponges
Current Intensity	Weak to strong sensation	Setting that is changed according to patient description. 'Strong but comfortable' is a common desirable setting
Treatment Duration	Variable Time	Settings can apply treatment for as little as one minute to 99 minutes in most cases.

1.6.2.2 Pain Relief

As previously discussed in section 1.5, which described the physiology involved in pain transmission, this is exploration of how IFT may work to reduce pain via four main mechanisms:

1. Gate Control Theory as proposed by Melzack and Wall (1965). This proposes that action potentials in the form of impulses, travelling along large diameter fibres, compete for access into the central ascending sensory tracts in the dorsal horn of the spinal cord with nociceptive impulses travelling along the smaller diameter nociceptive fibres. The larger fibres conduct at a faster rate, and therefore their action potentials close the 'pain gate' to the nociceptive signals travelling along these smaller fibres, thus stopping the pain' reaching a conscious level. Some authors have claimed that IFT can work in this way as it can be used to stimulate these large diameter fibres (De Domenico 1982; Goats 1990; Adedoyin 2002).
2. Descending Pain Inhibition pathways. This involves the inhibition of pain via endogenous opioids such as endorphins, dynorphins and enkephalins. These chemicals have similar characteristics to the chemical analgesic Morphine, and are intimately involved with the descending pain suppression system. The descending pain suppression system relies on the selective stimulation of small diameter nociceptive fibres (Walsh, 1997). Through the use of IFT it is thought possible to stimulate these fibres through use of a low frequency current with a pulse duration of between 100-200μs (DeDomenico, 1987 (Low 2000).
3. Physiological Block: This is a mechanism proposed to involve the inhibition of nociceptive impulses by blocking the A-delta and C fibres with use of frequencies above 50Hz. DeDomenico (1987) states that C fibres are capable of synchronous firing with an electrical stimulus that has a frequency that does not exceed approximately 15Hz. Anything greater than this usually results in the cessation of conduction of these nerve fibres. A-delta fibres are capable of firing with frequencies up to 40Hz. Therefore a stimulus of 50Hz (as it is greater than 40Hz) should cause these fibres to cease firing, as this is at a frequency

higher than A-delta fibres are capable of firing, thus creating an analgesic effect. This effect has been proposed (De Domenico 1982; Low 2000), although never proven.

4. Placebo (Walsh, 1997). The patients undergoing treatment could feel less pain just as a result of the level of technology involved (as IFT units are usually quite impressive). This may contribute to the 'cognitive dissonance theory' that Richardson (1994) proposes, whereby the basis of this theory is that the patient holds two beliefs that are 'psychologically inconsistent', thus creating dissonance. The patient will try to resolve this by altering their perception of their symptoms as well as attempting to please the therapist.

1.7 Conclusion

With limited amounts of work done on the effects of IFT on knee OA, it is planned to carry out a pilot study comparing the effects of this modality to a clinically relevant and easily applicable exercise regime commonly used in clinical practice. The combined effects of these two treatments will also be compared against a control group.

It is hoped this study will inform current physiotherapy practice, add weight to the current body of evidence currently backing these physiotherapeutic techniques and be one of the first studies to compare these two treatment modalities on a UK based clinical population.

This chapter has presented an overview of the use of IFT and exercise therapy with a description of current pain theories. The following chapter plans to review the current knowledge base surrounding the use of IFT and exercise therapy in the treatment of OA knee. The current knowledge base will guide the planning of a trial which plans to look at the effect of both interventions in the clinical setting.

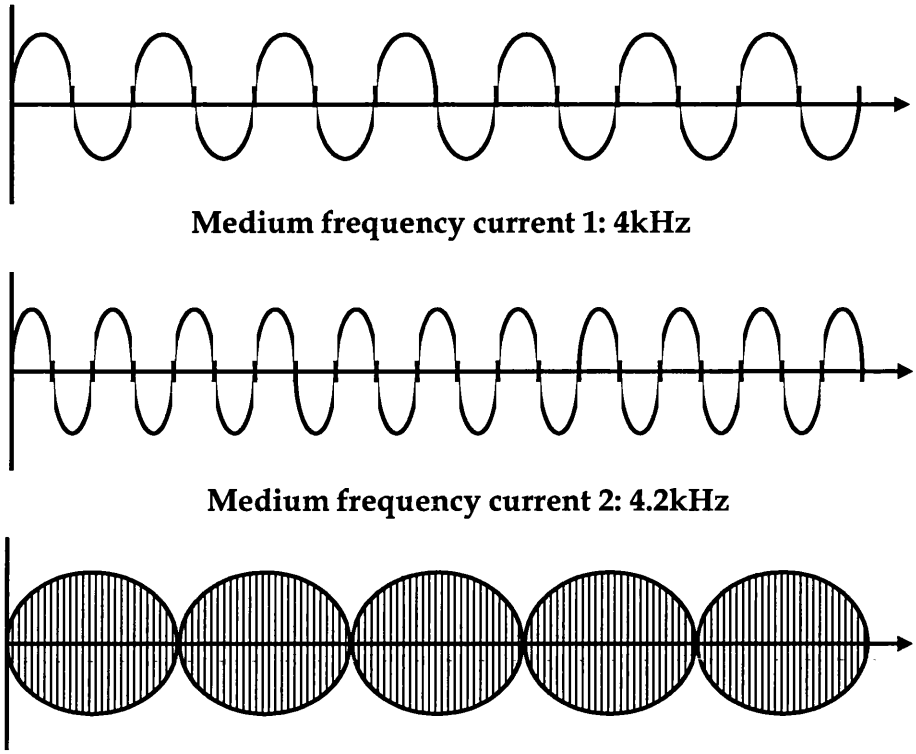


Figure 1: An illustration of the generation of interferential currents.

2.0 Literature Review

2.1 Abstract

Background: The use of exercise therapy is common in the treatment of osteoarthritis of the knee (Holden 2008). However, the use of IFT in the treatment of OA knee is less researched even though the modality is widely used (Pope 1995). The best types of exercise, dosage of exercise and frequency required to achieve pain relief and increased function remains unclear, as does a clear rationale for the use of IFT. It is the aim of this review to update the existing literature on the effect of IFT and exercise on osteoarthritis of the knee, and to try and establish the most effective exercises out of those that are commonly used.

Aims and Objectives: The aim of this review chapter is to examine the use of IFT and exercise therapy to ascertain the most effective usage in order to plan a future clinical trial. Method: A systematic review of English language articles using Medline, Web of Knowledge, Pubmed, and CINAHL between the years of 1970 and 2009 was undertaken. Eleven search terms were used in all. Search terms included Osteoarthritis, OA, Arthritis, Knee OA, Exercise, Exercise Therapy, Rehabilitation, Active Rehabilitation, Physical Therapy, Physiotherapy, and Physical Activity.

Study Selection: Only randomised controlled trials comparing the effect of exercise therapy with another intervention on knee OA were included. Studies were scored and included accordingly using the Pedro scoring system. Studies scoring seven out of ten or above were included in the review. Studies on the use of IFT were included following the use of key words to identify relevant studies. No scoring system was used in the identification of the IFT studies due to the relatively low numbers of studies currently published on the chosen area.

Data Extraction: Following identification through searching of key terms, abstracts of studies were screened to identify studies meeting the inclusion criteria. After studies had

met the inclusion criteria, scoring of exercise therapy based studies using the Pedro system was carried out to identify those with high methodological quality. Studies on the use of IFT were included on the discretion of the author.

Results: Of 124 exercise therapy based papers identified in the initial search using key terms, seventeen papers were selected for further critique. Eleven studies assessing the effect of IFT were chosen for review.

Limitations: Searches were carried out on the databases outlined above between the years of 1970 and 2009. Limits included were English language only. Efforts were made to attain all papers highlighted, however if full-text papers were not available, they were not used.

Conclusions: It appears that IFT is beneficial in the treatment of musculoskeletal complaints, however there seems to be no optimum settings described for the treatment of such conditions. Exercise therapy appears to be effective in reducing pain, improving strength and function in patients with knee OA. Furthermore, due to the wide variety of exercise protocols used, it is difficult to establish which exercises are most effective. However, it does appear that exercises targeting the quadriceps and hamstring muscle groups are among the most appropriate in this group of patients.

2.1 Chapter Introduction

This chapter contains a review of the current literature surrounding the use of IFT and exercise therapy of the knee. The chapter is split into a narrative review and systematic review based on the large amount of literature examining the use of exercise therapy in the treatment of OA knee, compared with the relatively scant amount of literature looking at the use of IFT in the treatment of OA knee.

2.2 Interferential Therapy Narrative Review

2.2.1 Introduction

With regards to the effective management of various musculoskeletal conditions, physiotherapy as a discipline is commonly employed, as physiotherapists have numerous modalities at their disposal to treat such disorders. The objective of this chapter is to provide an overview of one of the electrotherapeutic modalities commonly used to treat musculoskeletal conditions, namely Interferential Therapy (IFT). The review plans to look at the background of this electrotherapeutic modality and examine the evidence base (laboratory and clinical) relating to its effectiveness in managing musculoskeletal related pain, which is a common clinical feature in people with osteoarthritis. It is important to indicate that due to an extensive amount of previous investigations examining the effectiveness of electrotherapy focusing upon the effects of TENS, in comparison to the limited amount of IFT based research; this review plans to outline the general evidence surrounding the use of TENS and IFT in the treatment of musculoskeletal pain with more emphasis placed on the research surrounding IFT and musculoskeletal pain. However, it has been recognised that there are distinct physiological differences between TENS and IFT, and caution needs to be applied in extrapolating the evidence for TENS to IFT efficacy.

2.2.2 Popularity of IFT

IFT is a commonly used treatment employed by physiotherapists to treat a variety of musculoskeletal pain (Lindsay 1990). It is reported to be widely used (Pope 1995; Robertson 1998; Draper 2006) and effective at treating a wide variety of conditions. These include acute and chronic pain, stress incontinence and circulatory problems (DeDomenico 1987), recent injuries, herpes zoster, shoulder pain, incontinence and back lesions (Savage

1992). Despite the relatively popular use of the modality, the amount of research into its use remains relatively scarce and Johnson (1999) suggests that the level of evidence based upon the hierarchy of evidence (Hoeken 2009) needs to be considered as various studies are reports of anecdotal observations from clinical practice or in the form of descriptive studies using personal experience of experts in the field. Whilst Robertson (1998) further reports that the relatively common use of electrophysical agents (this includes IFT) is at a rate of one for every other treatment, the author concludes by asking why there is little documented evidence regarding its clinical effectiveness. Therefore, there is a need for more IFT specific research to support its continued clinical application with robust clinical research and cost effectiveness analysis.

2.2.3 Interferential Theory

An overview of the theory of the generation of IFT currents has been presented in the introductory chapter, section 1.6.2 and therefore a brief outline is now presented.
IFT is a type of electrotherapy that uses two alternating medium frequency currents which are applied simultaneously through interrelated electrodes. Medium frequency is applied via the electrodes to penetrate the skin surface as it is less painful than low current when applied to the skin. After penetrating the surface tissue, these currents are said to interfere with each other (essentially cancelling each other out) to produce a therapeutic low frequency current within the target tissue (Watson 2008). These individual currents are not strong enough to stimulate nerve and muscle directly until the amplitude is modulated by interference. This interference augments the currents to create a new frequency deep in the targeted tissues which works to try and reduce the pain sensation (Adedoyin 2002; Noble 2006). The frequency of the remaining current deep within the tissues is equal to the mean of the two original currents and will vary in amplitude at a frequency equal to the difference between these two currents. This latter frequency is known as the 'beat frequency' (Watson 2008).

2.2.4 IFT and the Pain theories

The clinical application of IFT is based upon attaining the following four goals:

1. Relieve pain
2. Stimulate Muscles
3. Increase blood flow
4. Reduce oedema

As this study plans to examine the affect of IFT on pain, this will be the main focus of the review. There are a number of mechanisms through which IFT is said to affect pain. Thesehave previously been outlined in section 1.5 of the study and therefore the reader is referred to this section for a description.

Although there are numerous theories as to how IFT may reduce pain, few studies have been done that are able to state with any significance that it is understood how IFT has an effect on any type of pain or to justify its use (Goats 1990).

2.2.5 Evidence Base

The degree to which electrotherapy and IFT achieves pain relief is widely debated and a brief overview on the effect they may have on pain relief within a variety of conditions is now presented.

Osiri (2000) presented a Cochrane review on the effect of TENS on pain relief in knee OA. In the review seven papers were analysed and the results presented. The review found that TENS was found to be effective over placebo for pain control. The review stated that at least four weeks of TENS treatment was needed to reduce both knee pain and knee stiffness. However, it was recommended that more well-designed studies with a standardised treatment protocol were needed before the full effects of TENS on knee OA could be concluded.

2.2.5.1 Laboratory Based Trials

Jorge (2006) examined the effect of IFT influence upon analgesia and inflammation in rats. In the study, sixty-nine rats were injected with formulae known to induce pain and inflammation separately. The pain response was measured on the basis of certain movements that rats display as a result of pain, e.g. flinching or retraction of the injected paw, or the 'freezing reaction'. Objective measures were taken as either counting the number of flinching movements the rat made, or the amount of time until either reaction was produced. In the study, the formula used to induce the acute pain was Formulin, and the formula used to induce inflammation was Carrageenan.

The Formulin was applied to the hind paw of the rat, and the number of nociceptive reactions was measured over the period of 1 hour, in 5-minute blocks. Carrageenan was used in combination with a syringe piston to induce pain. The piston was used to induce pressure onto the hind paw of the rats. The researchers measured a baseline period from the application of 20mmHg of pressure on the hind paw, up until the rat produced the 'freezing reaction'. This period of time served as the baseline response period. The researchers then injected the Carrageenan, and measured the same response 2, 3 and 4 hours after the injection application. The reason the reaction was measured over this time period was that Carrageenan is said to have maximum affect 3 hours after being injected. To test the effect of IFT application on pain, the rats were divided into seven groups; Group 1 received IFT before the Formulin injection, Group 2 received sham IFT before the injection, Group 3 received IFT immediately after the Formulin injection, Group 4 received sham IFT immediately after the Formulin injection, Group 5 received no intervention at all with a Formulin injection, Group 6 received IFT 2 hours after Carrageenan injection, and Group 7 received sham IFT 2 hours after Carrageenan injection. In all cases IFT was applied at a beat frequency of 140Hz constant, with a pulse duration of 125 milliseconds, and a carrier frequency of 4000Hz for 1 hour.

The results from the study indicated that the IFT applied immediately after the Formulin injection, significantly reduced the amount of nociceptive behaviour in the rats when

compared with the rats receiving sham IFT after the Formulin ($p=<0.05$). Furthermore, IFT applied in Group 6 reduced the nociceptive behaviour immediately after its application, however the reduction did not continue for the hour of application. Therefore, the study appears to show that application of IFT reduces inflammatory pain for the duration of time that it is applied, when compared to no treatment, or to sham IFT treatment. This study adds to the body of evidence supporting the use of IFT to reduce pain, and suggests that a frequency of 140Hz may be able to be used to achieve analgesia from inflammatory pain.However the characteristics of the sample group used reduces the external validity of the study as the successful application of IFT on rats may not translate when applied to humans. The study showed that IFT reduced pain for the duration of time that it was applied, but its lack of effect on swelling (as this was also measured in the study) means that the mechanism of pain relief is unlikely to be caused by the movement of inflammatory mediators which are known to induce pain. The study suggests that the pain relief as a result of IFT application is more likely to be caused by the Pain Gate Theory or Physiological Block as described previously. Additionally, the study adds to the research suggesting that IFT can have a beneficial effect on pain.

Some authors of studies involving the use of electrotherapy to produce pain relief argue that the mechanisms producing hypoalgesia are the same, regardless of the type of electrotherapy (i.e. TENS or IFT) used (Johnson 1999; Johnson 1999; Johnson 2003). This could have major financial implications as an IFT unit is significantly more expensive than a TENS unit. The following studies examine the use of these two modalities in the prevention of different types of pain.

Johnson (2003) compared the effect of two different electrotherapeutic modalities known to produce hypoalgesia on pain-free volunteers. In the study, the effects of TENS and IFT were compared on ischemic pain in 30 otherwise healthy volunteers. Each participant attended the research laboratory twice with a 24-48 hour interval in between. During the first visit, each volunteer had baseline data recorded. To achieve this data, subjects underwent a submaximal-effort tourniquet test (SETT). This involved attaching a sphygmomanometer to the subjects' forearm which was inflated to a pressure of

200mmHg. This was kept on for 12 minutes. During the first minute subjects were asked to perform 20, 75% hand squeeze contractions on a hand held device (this was determined through pre-test grip strength measurement) to induce ischemic pain. Subjects were asked to rate their pain every minute using a visual analogue scale (VAS) score. This is 10-point line marked on a piece of paper with the words 'no pain' at the number 0, leading up to the words 'worst pain imaginable' at the number 10. A post-test short-form Mcgill pain questionnaire was also used to measure pain after the procedure. During the second visit to the laboratory, subjects underwent the same procedure, but with 22-minutes of treatment which started 10 minutes 40seconds prior to the sphygmomanometer being inflated. The treatment was randomly allocated, with 10 subjects receiving IFT at a frequency of 100Hz, 10 subjects receiving TENS at a frequency of 100pps and 10 subjects receiving sham electrotherapy where electrodes were placed on the skin, with no current being passed. The authors found that the IFT produced a significant reduction in pain ($p=<0.05$) when compared to the sham electrotherapy, but not when compared to the TENS. The pain reduction induced by the TENS was reported to be insignificant ($p=0.06$) when compared to sham treatment. Even though the authors document this finding, in the discussion the authors postulate that 'IFC (IFT) is at least as effective as TENS when delivered to produce a strong but comfortable electrical paraesthesia within the site of pain', and furthermore that it may be more effective to use TENS rather than IFC'. These claims suggest an element of bias toward the use of TENS as the study carried out shows that IFT produces a significant reduction of pain, and TENS does not when compared to sham electrotherapy. This study is another that adds to the body of evidence suggesting that IFT used at a frequency of 100Hz could have a significant effect on the reduction of pain. However, it is another study that does not fully explain the mechanism through which IFT operates to produce hypoalgesia.

Johnson (1999) carried out a double blind, randomised controlled study comparing the effect of IFT and TENS on cold induced pain. A convenience sample of 21 was used in the study. The sample was split into three groups, with the first group receiving IFT as the treatment, the second receiving TENS, and the third receiving sham treatment. All subjects had to place their hand in warm water for five minutes, then into ice cold water. The time

taken for the subject to say 'pain' was used as their pain threshold. The subject then had to keep their hand in the water for a further 30 seconds before removing their hand. On removal they were asked to rate the pain and unpleasantness of the sensation on a scale of 0-10. This constituted one cycle. All subjects completed six cycles, with the intervention being applied for the third and fourth cycles. IFT delivered in the study was bipolar at a modulated frequency of 100Hz and at a strong, but comfortable intensity. This setting was based on previous work carried out by the authors. Sham IFT was used to maintain blinding in the study. Additionally, TENS was delivered at 100Hz. Subjects in the sham group received no stimulation but watched an oscilloscope display which changed frequently giving the impression that a current was being delivered.

The study found that subjects in the IFT and TENS groups demonstrated significantly higher pain thresholds than those in the sham group ($p=<0.05$). However, there were no significant differences between these two groups. None of the groups demonstrated any significant changes in pain intensity or unpleasantness rating. Even so, this study does demonstrate that both electrotherapeutic modalities seem to have an effect on pain threshold, even though this study failed to demonstrate whether one modality is more effective than the other. The study also adds to the varying types of pain that IFT appears to have analgesic effects on when used at a frequency of 100Hz. The following study again examines the effect of IFT delivered at 100Hz on various types of pain.

Mcmanus (2006) examined the analgesic effects of IFT on pain induced by different methods; through temperature variation and mechanical irritation. Twenty subjects were used in a cross-over randomised, controlled trial. Subjects were split into two groups of 10 and were randomly assigned to receive mechanical pain or cold-induced pain initially, then to receive the opposite pain type in the following phase of the study. For cold-induced pain, subjects had to immerse their hand in a bowl of ice cold water, after having the hand in warm water. The subject had to say when they felt pain after immersion in cold water; the time it took for the subject to say 'pain' was taken as their cold-pain threshold. Thirty seconds after this, the subject removed their hand from the cold water and rated the intensity and unpleasantness of the pain on a scale of 0-10. The subjects then rested for the

remainder of the 10-minute cycle, before repeating the procedure 6 times. During cycles 3 and 4 of the process, IFT was applied for 20minutes at a frequency of 100Hz.

Mechanical pain was applied via a clamp with an electrode measuring the amount of force placed through the clamp. Subjects in this group had the clamp applied to the webspace of their index finger and thumb. The subjects manually tightened the clamp, and on experiencing pain, said the word "pain". The amount of pressure was recorded and the subject then gradually increased the pain to a maximal sustainable level. This level was recorded and the subject was free to gradually release the pressure. The subject rated their unpleasantness of pain on a scale of 0-10, and then rested for the remainder of the cycle. As with the cold-induced pain, there were six cycles of pain application, with the IFT being applied for the 3rd and 4th cycles for 20minutes in total. IFT was applied via two electrodes placed on the anterior and posterior aspect of the forearm, midway between the wrist and elbow for both pain inducing procedures.

The study reports that IFT had a significant effect on the pain threshold in both aspects of pain induction (*p=0.017- cold, p=0.041- mechanical*). In addition, it was demonstrated that it took a significantly greater amount of time for subjects to report pain in the cold-induced pain model, and the amount of pressure needed to induce pain was significantly greater in the pressure model when subjects were receiving IFT. However, in the study subjects will have known when the IFT was being applied, and therefore, it could be questioned as to whether they would be more likely to alter their behaviour. The conditions during whichthe subjects were receiving the IFT were not commented on. The setup of the trial was very experimental, thus the 'clinical' relevance of the trial could be questioned. The sample size of the population studied could be considered as being limited, and this in conjunction with the fact that the sample population were of convenience in a university population, may reduce the ability to generalise the results of the study. However, the study does add to the body of evidence concerning IFT and pain relief.

Summary Table of Laboratory Based Trials (See Table 5)

2.2.5.2 Clinical Trials

Cheing (2002) examined the effect of exercise and/or TENS on knee OA with pain as the main outcome measure. Sixty-two patients with knee OA were split into four groups; one receiving TENS, one receiving placebo TENS, one receiving exercise therapy, and the final group receiving TENS and exercise. The main outcome measure was the visual analogue scale (VAS), which is a subjective measure of pain. Subjects in the study received treatment five days a week for four weeks, which consisted of 60 minutes of TENS each treatment session at a frequency of 80Hz.. Those in the placebo group had electrodes placed in the same place, and had TENS units with lights on, but with no internal unit to ensure that no stimulation was provided via the unit. Subjects in the exercise group received quadriceps and hamstring strengthening exercises on an isokinetic dynamometer. Those in the combination group received 60 minutes of TENS followed by 20 minutes of exercise.

The study reported that all groups had a significant reduction in pain during the four week period of the study. However, in the period between the final treatment and the final data collection (four weeks), there was a significant increase in pain in the exercise only and placebo groups, which suggests a limited carry-over of pain relief effect for these groups. This study adds to the evidence suggesting that combinations of electrotherapy and exercise, as well as TENS alone can have a significant effect on pain experienced with knee OA. However, in the study, only one outcome measure was used, and the reliability of this measure has been questioned (Carlsson 1983). The amount of treatment subjects received in the study may also be questioned as it is not common practice to treat patients as often or for as long.

In a later study, Cheing (2004) examined the effect of the same procedure on different outcome measures. In this study, 66 subjects with radiographically confirmed knee OA were randomly assigned to receive TENS, placebo TENS, exercise or a combination of

TENS and exercise. In this study, the functional effects of the four treatments modalities were assessed. Overall the study found that those receiving TENS produced improvements in gait parameters ($p=0.053$). Furthermore, those in the TENS group and exercise group produced significantly improved force of knee extensors with the knee at 60 or 90 degrees flexion ($p=0.013$, $p=0.001$). The group receiving a combination of treatments produced the greatest improvements in force generation ($p=0.002$), gait parameters ($p=0.006$) and range of movement ($p<0.001$) of all the groups, and greater improvements than those receiving each treatment in isolation. Therefore, this study again demonstrates the positive effect of combined electrotherapy and exercise treatment on the functional difficulties experienced with knee OA. However, the study does employ treatment methods/approaches that would be uncharacteristic for traditional physiotherapy departments due to the equipment used for treatment, and frequency and length of treatment. Another study that examined the use of combination therapy in the treatment of a musculoskeletal complaint was the following study by Hurley et al. (2004).

Hurley (2004) compared the individual and combined effects of manipulative therapy and IFT on Low Back Pain (LBP). In this study, a large number of subjects presenting with acute LBP were randomly assigned to receive manipulative therapy (MT), IFT or both. There was no control group used. All subjects received The Back Book, as well as their randomised intervention. Subjects in the MT group were treated with mobilisation or manipulation at the discretion of the treating physiotherapist. The study ensured that all treating physiotherapists were of a high standard by only including those with post-graduate study. Subjects in the IFT group received 30 minutes of IFT at a frequency of 140 Hz constant. Subjects were treated an average of five times, over five weeks. Outcomes used measured pain, function, and quality of life and subjects were followed up for a period of twelve months. The study found that there was a 'clinical improvement' in all groups, in all outcome measures, although there was no significant difference between groups. The combined therapy group showed a significant improvement when compared to manual therapy for physical functioning ($p=0.04$) and bodily pain ($p=0.036$).

It was stated in a previous study by the same authors, that the same IFT method when compared to The Back Book yielded significantly better results in terms of functional disability, even though this was a preliminary study (Hurley 2001). Therefore, overall this study, along with those previously reviewed, add to the body of evidence supporting the use of combined therapy involving IFT in the clinical environment when the goal is pain relief. The study also adds to those using IFT at a frequency above 140Hz and according to theories stated in section 1.5, possibly utilizing the physiological pain block or pain gate mechanisms.

Walker (2006) looked at the effects of IFT on psoriatic arthritis. The outcome measures utilised in this study were pain, morning stiffness, physician and patient assessed disease activities, function, blood sedimentation rates (BSR) and C-reactive protein (CRP). Radiological investigation in the form of X-ray and MRI were also carried out on the hands and feet of subjects and scored on different criteria indicating joint inflammation and degeneration. Nine patients were treated with home-use, bipolar IFT units. They were advised to place the electrodes on their hands and feet, while immersed in water. Subjects were told to apply the IFT for 5 minutes in the morning at a frequency of 100Hz, and 5 minutes in the evening at 10Hz, at a comfortable intensity. This treatment protocol was carried out daily for 16 weeks. Results found that there was a high adherence to treatment, although there were minimal significant changes. It was found that in the SF-36 (a function scale), the sub-group for pain showed a significant improvement ($p=0.03$), although the VAS scales used failed to show this. There was a significant improvement found in morning stiffness ($p=0.02$), as this reduced from a mean of 38 minutes to 4 minutes. Joint tenderness was the only other significant improvement found in the study ($p=0.04$). Further outcome measure changes were not to a significant level. This study was a pilot-study, thus had a small sample group, and therefore the findings cannot be applied generally. However, the study does seem to add to the argument that IFT can have a significant effect on pain even though the subjects were only using the IFT for 10 minutes a day, and for half of that time, at a frequency that is not known to produce analgesia.

Jarit (2003) examined the effect of IFT on pain, swelling and movement on post-operative knees. The study was a double-blinded RCT and found that IFT had a significantly positive effect on all three outcomes measured. The study did not include a functional assessment as an outcome. Outcome measures were looked at from the stage immediately post-operatively up until nine weeks post surgery. In the study, all patients had undergone knee surgery, however the type of surgery and the surgeon varied, thus reducing the validity of the study. The types of surgery included either: Anterior Cruciate Ligament (ACL) reconstruction, meniscectomy, or knee chondroplasty. Within each type of surgery, patients were randomly assigned to either receive home IFT or sham IFT (placebo). All subjects received a standard physiotherapy protocol, as well as their allocated treatment during their post-op recovery period. Subjects were instructed to use the IFT units three times a day, for 28 minutes each session for 7-9 weeks. This amount of treatment would be realistic if patients were to use home IFT units, however in the majority of hospital departments in the UK, IFT units are for department use only, thus this amount of treatment would be unrealistic. The placebo group was advised to turn on the unit for 30 minutes, three times per day. They were advised not to be alarmed if no sensation was felt.

This study claims to show a significant benefit of using IFT on post-operative knee surgery patients. However, in the study there was no confidence interval stated, and no p values given for any results. There is no statistical analysis section published and this makes analysis of the results difficult. Due to the fact that the overall group was essentially split into the three sub-groups of surgery type, the number of subjects is greatly reduced, thus reducing the external validity of the study, and thus the ability to accurately predict these values in the general population. Furthermore, there was no functional outcome used however all other outcomes were appropriate and commonly used in the clinical environment. The method of placebo application in the study has to be questioned , as over a period of nine weeks a subject is likely to suspect that they would be receiving a placebo. A superior model of control might have used a stimulus that would be unlikely to affect pain or swelling, even though this would also constitute a method of intervention. The study followed up the effects for a relatively long period, and therefore this study could add

to the body of evidence for the use of IFT to reduce inflammatory pain, however due to the lack of key information it is difficult to interpret its results with any amount of accuracy.

The effect of IFT on knee OA has been studied by (Adedoyin 2002; Adedoyin 2005). In the former, the effect of IFT on knee OA in an African population was studied in isolation. Subjects were recruited if they had radiologically confirmed knee OA. All subjects did underwent a screening of their lower quarter to ensure the pain did not originate in any other major joint of the lower limb. Thirty subjects were recruited to the study and were allocated to an IFT group or a placebo group. Allocation was not randomised, although stratification of patients did take place to ensure equal distribution of age, height, weight and BMI. All patients were asked to change their diet prior to the study, although the reason for this was not explained. Subjects in the IFT group received treatment twice a week for 4 weeks. IFT was applied at a frequency of 100Hz for the first 15minutes of treatment, followed by 5 minutes of treatment at 80Hz at a comfortable intensity. IFT was applied via a quadrapolar method ensuring that current was directed at the centre of the knee joint. In the placebo group, subjects were attached to the IFT machines in the same way, although instead of the intensity being at a comfortable intensity, the machine was not turned up at all. The main outcome measure used in the study was pain rating with the Visual Analogue Scale (VAS), and this was assessed before every treatment. Although this scale has been proven to be a reliable outcome measure (Scrimshaw 2001; Geier 2007), by asking subjects prior to every treatment session, there could be seen to be an increased pressure on the subject to 'get better', as they would be more likely to remember the answer they gave to the same question previously, furthermore it has been proven that the VAS is less responsive than other measures when used to rate current pain in comparison with over the last 24 hours (Scrimshaw 2001). There was no functional measure used as an outcome, although this was recognised in the discussion. Overall, the study stated a significant improvement in pain in both the IFT and placebo groups, however no p-values are published, and therefore the results of this study must be interpreted with caution. Furthermore, the placebo could be questioned as a method of control, as the patient could still be experiencing some sort of stimulation, albeit at a very low intensity. It is also stated that subjects received a morning treatment, and a twice weekly exercise regime, although it

is not explained what this treatment was, or what exercises were used, therefore any improvement could be due to other interventions. This study does not really add to the argument that IFT is beneficial for pain relief as the significance of the result is unknown, and also contributes minimally to the mechanism of the action of IFT.

In the second study by the same author (Adedoyin 2005) forty-six subjects with radiologically confirmed knee OA were recruited to compare the effects of IFT and TENS on knee OA. The sample size was based on a power calculation done prior to the study. However, when calculating, an assumption was made that a significant change in VAS score would be 30%. This could be questioned, as there appears to be no scientific basis for this assumption. In the study, the WOMAC scale of function was used as the main outcome measure, with pain as a secondary measure. The same assessor was used throughout the study to assess both outcomes, increasing the validity of the study. To reduce any possible psychological effect on patients, a machine that delivered TENS and IFT was used to deliver the allocated treatment. This was a positive aspect of the study as it has been claimed by other authors that the more impressive appearance of an IFT machine could be a possible reason for the effect of treatment (DeDomenico 1987). In the study, subjects were randomly allocated to one of three groups. One group received IFT and exercise, one received TENS and exercise, with the remaining group receiving exercise alone. Each subject had their own exercise programme in the study as the weight that they were required to lift progressed according to their own maximum repetition. In the IFT group, subjects were treated twice a week, for 4 weeks. IFT was applied at 80Hz continuous for 20 minutes at a comfortable level. TENS was applied for the same amount of time, with the same treatment frequency (80Hz) and a phase duration of 200ms. The study found that there were statistically significant improvements for all groups in pain ($p=0.001$) and WOMAC scores ($p=0.001$) for all groups, however, there were no statistically significant differences between groups. The study adds to the evidence that IFT at or above 80Hz appears to have a significant affect on pain, however this study suggests that it is no more effective than exercise alone or exercise combined with TENS.

For Summary Table of Clinical Based IFT Trials, see Table 6

2.2.7 Summary of IFT Studies

In summary, studies evaluating the effect of IFT are low in number and methodological quality. However, the studies reviewed appear to show a positive effect of IFT on pain relief when used at frequencies above 80Hz. Mechanisms that are thought to take place when IFT is applied to pain seem to be poorly understood and seem to be based more on opinion of experts in the field than fact (Johnson 1999), however due to the positive results of studies reviewed that utilized frequencies above 80Hz, it may be postulated that physiological pain block or pain gate mechanisms may be accessed with IFT at these frequencies.The research methodologies utilised make it difficult for an overall consensus of opinion to be achieved as many of the studies use different treatment parameters, such as varying timescales of application, and measure different outcomes. However, the research that has been carried out seems to be in favor of IFT when treating pain for a variety of pathologies, and there appears to be a need for more randomised controlled trials to evaluate the true effectiveness of IFT (Johnson 1999). The following section of the review chapter will examine the use of exercise therapy in the treatment of OA knee.

2.3 Exercise Therapy Review

2.3.1 Introduction

OA of the knee is a major contributor to functional impairment and reduced independence in older adults, commonly affecting adults over the age of 45 (Peat et al., 2001). Osteoarthritis most commonly affects the joints of the lower limb, in particular the hip and the knee, with the knee being the most commonly affected (Felson 1987; Mcalindon 1992; Sisto 2006). Due to the average age of the population gradually increasing the number of people suffering with the disease, along with the cost of treatment is also likely to increase (Rat 2005).

There are many surgical options for the treatment of knee OA including arthroscopy, joint lavage and knee replacement, however these methods are costly and tend to be used as a 'last resort'(Zhang 2007). Therefore, a commonly used method of treating OA, due to its relatively low cost and convenience is physiotherapy, and one of the main forms of physiotherapeutic treatment that is utilised is exercise therapy (Holden 2008).
Various reviews have been carried out on exercise therapy in the treatment of knee OA (Fransen 2001; Roddy 2005; Holden 2008), and various others have recommended exercise be used in the management of the knee OA (Jordan 2003; Zhang 2007). The benefits of exercise to those with knee OA are said to include improved function, reduced pain, improved walking speed and improved strength (Ytterberg 1994; Van Baar 1999; Vad 2002; Thorstensson 2005). However, although many benefits of exercise have been agreed, there is less consensus on frequency of exercise, exact types of exercise and exercise dosage (Holden 2008). A recent study (Roddy 2005) did outline the benefits of specific types of exercise, the benefits of different exercise situations (group vs home), the importance of adherence and different strategies to improve this. The review was based on research evidence and on recommendations of a panel of ten experts in the area. The study highlighted the need for further research on the practicalities of carrying out exercise as a treatment, i.e. exact modes of exercise, contraindications etc.

2.3.1.1 Objective

The aim of this review is to outline the studies that have been done in this area in the context of the overall thesis and to add to the database of knowledge on the area by updating with reviews recently carried out, with the overall aim being to establish the effect of exercise therapy on knee OA, and the most beneficial methods of application to guide a future clinical study into the area.

2.3.2 Method

In order to understand the current level of knowledge of the potential clinical benefits of exercise therapy programmes for the effective treatment of osteoarthritis of the knee, a number of methods were employed to identify the relevant literature. Electronic searches, hand searches and a quality criterion were employed in order to perform a rigorous and expansive search of all the available and relevant peer-reviewed literature. Furthermore, non-peer reviewed information was collected and reviewed for relevance to the overall discussion.

2.3.2.1 Search Strategy and Electronic searches

Relevant trials and reviews were identified by conducting electronic searches through Medline/PubMed, ISI Web of Knowledge, and CINAHL databases. A preliminary search of electrotherapy literature was conducted in order to highlight key phrases to facilitate a more categorical search; these included:

- Osteoarthritis (and any deviation of it such as OA)
- Exercise
- Exercise therapy
- Rehabilitation
- Active rehabilitation
- Physical therapy
- Physiotherapy
- Physical activity

Due to the large number of papers retrieved from the databases, the searches were limited to studies of human subjects, published in the English language and in the last 40 years.

Keywords were individually searched, and then combined in order to locate a number of the most relevant trials.

The same process (i.e. combining keywords and limiting searches) was conducted on the all electronic databases between the search dates of 1970 and 2009, the results of which are in table 1 which shows the number of papers retrieved from all electronic databases, with each keyword and their combinations.

The abstracts of the papers yielded by searches using the different keyword combinations were read and appraised to decide the two final search phrases (i.e. eligibility and quality assessment). It ensured that the papers were relevant to the overall objective of the project, which is to explore the research evidence for the therapeutic benefits of exercise therapy in people living with osteoarthritis of the knee, within the context of the existing evidence base.

2.3.2.2 Inclusion Criteria

Papers were included if they were published in the date ranges identified, they compared land based exercise with any other intervention in the treatment with OA of the knee, and if the full-text of the paper was available.

2.3.2.3 Hand searching

The reference lists of the relevant papers found through the electronic database searches were then checked for further relevant papers. A number of relevant Cochrane library publications were found amongst the appraised papers' references. Efforts were therefore made to retrieve these papers through the Cochrane database.

2.3.2.4 Quality criterion

The 'PEDro scale' was used to appraise the papers as a further criteria for inclusion in order to consider the internal validity of the trials, and to discover if there was sufficient statistical information to make the results interpretable. The PEDro scale consists of a checklist of 11 conditions and gives a total possible score of 10 if all 11 conditions are fulfilled. Criterion numbers 1 to 8 assess internal validity and give a score out of 8. Criterion numbers 9 and 10 assess statistical reporting and give a score out of 2. Criterion number 11 is not used to calculate the PEDro score, but has been included in the PEDro scale so that all items of the Delphi scale are represented. Papers were only included if a combined score of 7 or above was prescribed, ensuring that only robust papers conducted to a high quality were included in the systematic review.

Tables 2 and 3 show the PEDro scale and marking criteria with which papers were appraised.

Table 2:- Criteria and explanations

1. Subjects were randomly allocated to groups **Explanation** Random allocation ensures that (within the constraints provided by chance) treatment and control groups are comparable.	no/yes
2. Allocation was concealed. **Explanation** "Concealment" ensures that there is no systematic bias due to the person who determined if subjects were eligible for inclusion in the trial being aware, at the time he or she made this decision, which group the next subject would be allocated to.	no/yes
3. The groups were similar at baseline regarding the most important prognostic indicators. **Explanation** This criterion may provide an indication of potential bias arising by chance with random allocation. Gross discrepancies between groups may be indicative of inadequate randomisation procedures and lead to bias treatment outcomes.	no/yes
4. There was blinding of all Subjects **Explanation** Blinding of subjects involves ensuring that they are unable to distinguish whether they received or did not receive the treatment. When subjects have been blinded, the reader can be satisfied that the apparent effect (or lack of effect) of treatment was not due to placebo effects or Hawthorne effects (whereby participants responses are distorted by being observed and how they expect the experimenters want them to respond).	no/yes

5. There was blinding of all therapists who administered the therapy **Explanation** Blinding of therapists involves ensuring that they are unable to distinguish whether individual subjects received or did not receive the treatment. When therapists have been blinded, the reader can be satisfied that the apparent effect (or lack of effect) of treatment was not due to the therapists' enthusiasm or lack of enthusiasm for the treatment or control conditions.	no/yes
6. There was blinding of all assessors who measured at least one key outcome. **Explanation** Blinding of assessors involves ensuring that assessors were unable to distinguish whether individual subjects received or did not receive the treatment. In trials in which key outcomes are self-reported, visual analogue scale or pain diary for example, the assessor is considered to be blind if the participant was blind. When assessors have been blinded, the reader can be satisfied that the apparent effect (or lack of effect) of treatment was not due to the assessors' biases impinging on their measures of outcomes.	no/yes
7. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups. **Explanation** It is important that measurement of outcome is from as many subjects who are randomised to groups as possible. Subjects who are not followed up may potentially introduce bias since they may differ systematically from those who remain in the study. The magnitude of the potential bias increases with the proportion of subjects not followed up.	no/yes
8. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat". **Explanation** Almost inevitably there are protocol violations in clinical trials, which may involve subjects not receiving treatment as planned or receiving treatment when they should not have. Biases may be produced by analysis of data according to how subjects were treated (rather than according to how subjects should have been treated). It is important that, when the data are analysed, analysis is done as if each subject received the treatment or control condition as planned. This is usually referred to as "analysis by intention to treat".	no/yes
9. The results of between-group statistical comparisons are reported for at	no/yes

least one key outcome. **Explanation** In clinical trials, statistical tests are performed to determine if the difference between groups is greater than can plausibly be attributed to chance.	
10. The study provides both point measures and measures of variability for at least one key outcome. **Explanation** Clinical trials potentially provide relatively unbiased estimates of the size of treatment effects. The best estimate (point estimate) of the treatment effect is the difference between (or ratio of) the outcomes of treatment and control groups. A measure of the degree of uncertainty associated with this estimate can only be calculated if the study provides measures of variability.	no/yes
11. Eligibility criteria were specified. **Explanation** This criterion influences external validity, but not the internal or statistical validity of the trial. It has been included in the PEDro scale so that all items of the Delphi scale are represented on the PEDro scale, but is not used to calculate the PEDro score.	no/yes

(http://www.otseeker.com/PDF/PEDroScalePartitionedGuidelinesExplanations.pdf)

Table 3:- Scoring Criteria:

All Criteria	Points are only awarded when a criterion is clearly satisfied. If on a literal reading of the trial report it is possible that a criterion was not satisfied, a point should not be awarded for that criterion.
Criterion 1	A study is considered to have used random allocation if the report states that allocation was random. The precise method of randomisation need not be specified. Procedures such as coin-tossing and dice-rolling should be considered random. Quasi-randomised allocation procedures such as allocation by hospital record number or birth date, or alternation, do not satisfy this criterion.
Criterion 2	Concealed allocation means that the person who determined if a subject was eligible for inclusion in the trial was unaware, when this decision was made, of which group the subject would be allocated to. A point is awarded for this criterion, even if it is not stated that allocation was concealed, when the report states that allocation was by sealed opaque envelopes or that allocation involved contacting the holder of the allocation schedule who was "off-site".

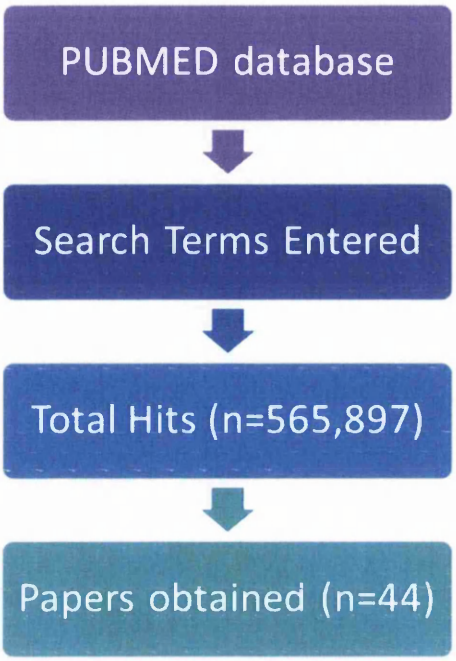
Criterion 3	At a minimum, in studies of therapeutic interventions, the report must describe at least one measure of the severity of the condition being treated and at least one (different) key outcome measure at baseline. The rater must be satisfied that the groups' outcomes would not be expected to differ, on the basis of baseline differences in prognostic variables alone, by a clinically significant amount. This criterion is satisfied even if only baseline data of study completers are presented.
Criterion 3, 6-10	Key outcomes are those outcomes that provide the primary measure of the effectiveness (or lack of effectiveness) of the therapy. In most studies, more than one variable is used as an outcome measure.
Criterion 4-6	Blinding means the person in question (subject, therapist or assessor) did not know which group the subject had been allocated to. In addition, subjects and therapists are only considered to be "blind" if it could be expected that they would have been unable to distinguish between the treatments applied to different groups. In trials in which key outcomes are self-reported (eg, visual analogue scale, pain diary), the assessor is considered to be blind if the subject was blind.
Criterion 7	This criterion is only satisfied if the report explicitly states both the number of subjects initially allocated to groups and the number of subjects from whom key outcome measures were obtained. In trials in which outcomes are measured at several points in time, a key outcome must have been measured in more than 85% of subjects at one of those points in time.
Criterion 8	An intention to treat analysis means that, where subjects did not receive treatment (or the control condition) as allocated, and where measures of outcomes were available. The analysis was performed as if subjects received the treatment (or control condition) they were allocated to. This criterion is satisfied, even if there is no mention of analysis by intention to treat, if the report explicitly states that all subjects received treatment or control conditions as allocated.
Criterion 9	A between-group statistical comparison involves statistical comparison of one group with another. Depending on the design of the study, this may involve comparison of two or more treatments, or comparison of treatment with a control condition. The analysis may be a simple comparison of outcomes measured after the treatment was administered, or a comparison of the change in one group with the change in another (when a factorial analysis of variance has been used to analyse the data, the latter is often reported as a group x time interaction). The

	comparison may be in the form of hypothesis testing (which provides a "p" value, describing the probability that the groups differed only by chance) or in the form of an estimate (for example, the mean or median difference, or a difference in proportions, or number needed to treat, or a relative risk or hazard ratio) and its confidence interval.
Criterion 10	A point measure is a measure of the size of the treatment effect. The treatment effect may be described as a difference in group outcomes, or as the outcome in (each of) all groups. Measures of variability include standard deviations, standard errors, confidence intervals, interquartile ranges (or other quantile ranges), and ranges. Point measures and/or measures of variability may be provided graphically (for example, Standard Deviations may be given as error bars in a figure) as long as it is clear what is being graphed (for example, as long as it is clear whether error bars represent Standard Deviations or Standard Errors). Where outcomes are categorical, this criterion is considered to have been met if the number of subjects in each category is given for each group.
Criterion 11	This criterion is satisfied if the report describes the source of subjects and a list of criteria used to determine who was eligible to participate in the study.

2.3.3 Results

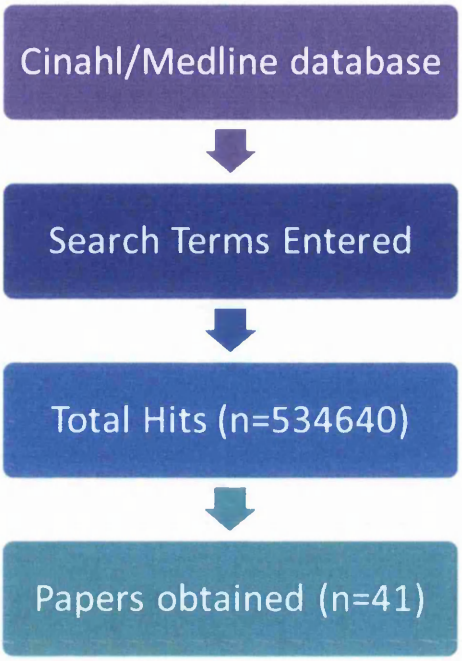
Below are the tables showing the number of papers retrieved, with each keyword and their combinations, from the PubMed database, ISI Web of Knowledge database, and CINAHL between the search dates of 1970 and 2009 (For full search results, please refer to Appendix 1).

Search Flow Chart 1; PUBMED database:



Search Flow Chart 2; Web of Knowledge Database

Search Flow Chart 3; Medline Database



Additionally, two reviewers scored papers using the scale and any disagreements were resolved by consensus. Papers scoring seven out of ten, or above were deemed eligible for inclusion in the systematic review.

The table below (Table 4) outlines the papers included in the review and the PEDro scores achieved during the scoring process:

Table 4: PEDro scoring table

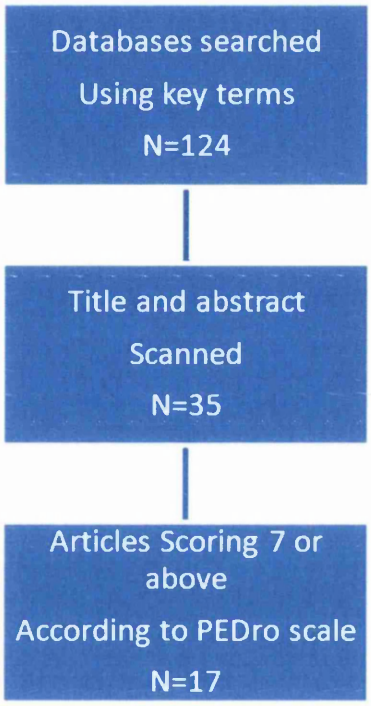
Authors	Title	PEDro Score
Williamson, L. et al. (2007)	Severe knee osteoarthritis: a randomized controlled trial of acupuncture, physiotherapy and standard management for patients awaiting knee replacement	8/10
Bennell, K.L. et al. (2005)	Efficacy of physiotherapy management of knee joint osteoarthritis: a randomised, double blind, placebo controlled trial	8/10
Chaipinyo, K. and Karoonsupcharoen, O. (2009)	No difference between home-based strength training and home-based balance training on pain in patients with knee osteoarthritis: a randomised trial	7/10
Deyle, G.D. et al. (2000)	Effectiveness of manual physical therapy	9/10

	and exercise in osteoarthritis of the knee	
Deyle, G.D. et al. (2005)	Physical therapy treatment effectiveness for osteoarthritis of the knee: A randomized comparison of supervised clinical exercise and manual therapy procedures versus a home exercise programme	9/10
Doi, T. et al. (2008)	Effect of home exercise of quadriceps on knee osteoarthritis compared with non-steroidal anti-inflammatory drugs	7/10
Thomas, K.S. et al. (2002)	Home based exercise programme for knee pain and knee osteoarthritis: randomised controlled trial	8/10
O'Reilly, S.C. et al. (1999)	Effectiveness of home exercise on pain and disability from osteoarthritis of the knee: a randomised controlled trial	7/10
McCarthy, C.J. et al. (2004)	Supplementing a home exercise programme with a class-based exercise programme is more effective than home exercise alone in the treatment of knee osteoarthritis	8/10
Jan, M.H. et al. (2008)	Investigation of clinical effects of high and low resistance training for patients with knee osteoarthritis: A randomised controlled trial	8/10
Huang, M.H. et al. (2003)	A comparison of various therapeutic exercises on the functional status of patients with knee osteoarthritis	7/10
Huang, M.H. et al. (2005)	Preliminary results of integrated therapy for patients with knee osteoarthritis	7/10
Karatosun, V. et al. (2006)	Intra-articular hyaluranic acid compared with progressive knee exercises in osteoarthritis of the knee: a prospective randomised trial with long-term follow up	8/10
Maurer, B.T. et al. (1990)	Osteoarthritis of the knee: Isokinetic quadriceps exercise versus an educational intervention	7/10
Ettinger, W.H. et al. (1997)	A randomised trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis.	9/10
Rogind, H. et al. (1998)	The effects of a physical training program on patients with osteoarthritis of the knees	7/10
Van Baar, M.E. et al. (2001)	Effectiveness of exercise in patients with osteoarthritis of hip or knee: nine-months follow up	8/10

In agreement with the paper inclusion criteria outlined in methodology section above, the original 35 papers yielded by the various searches, were narrowed to 17 when reviewed against the PEDro scale. The following eighteen papers were not included following scoring according to the PEDro scale: (Hurley 1998; Cheing 2002; Evcik 2002; Gur 2002;

Topp 2002; Cheing 2004; Eyigor 2004; Adedoyin 2005; Sekir 2005; Thorstensson 2005; Andersson 2006; Mikesky 2006; Veenhof 2006; Iwamoto 2007; Thorstensson 2007; King 2008; Shakoor 2008; Tsauo 2008)

Search Flow Chart 4: Overall search



2.3.4 Discussion

Williamson et al. (2007) carried out an assessor-blinded and randomised controlled trial that compared the therapeutic effects of acupuncture, supervised exercise and 'standard management' on a cohort of patients (n=181) awaiting knee arthroplasty (total, unilateral and bilateral). As a result, subjects were recruited from waiting lists and the demographic characteristics indicated little difference between participants in each of the groups. In this study, the acupuncture cohort (n=60) received once per week musculoskeletal acupuncture at defined points for 20mins for a total of 6 weeks; whilst the physiotherapy group (n=60) received a group based exercise based intervention; defined as static quadriceps contractions, inner range quadriceps contractions; straight leg raises, sit to stand, stair

climbing, calf stretches, theraband resisted knee extensions, balance training, knee flexion/extension and freestanding peddle revolutions. The control group (n=61) received a purposefully designed exercise and advice leaflet. The authors utilised a number of validated and reliable outcome measures that aimed to explore physical function (i.e. Oxford Knee Score questionnaire, the 50m timed walk test and WOMAC), pain (i.e. VAS), depression (i.e. HADS) and impact upon patient recovery and hospital resources (i.e. total length of stay post –operation) at repeated times for a period of baseline, 7 weeks, 12 weeks and 3 months post-operatively. The main results of the study indicated that acupuncture produced a significant short-term therapeutic reduction in the Oxford Knee Score for acupuncture at the 7 week time measurement only ($p = 0.0497$). Therefore, suggesting that the physiotherapy led group exercise intervention did not produce any statistically significant impact upon any of the outcome measures. The PEDro assessment of this paper indicated a 7 out of 10 score, which highlighted that this study was a randomised control trial with a power calculated sample size with blinded assessment with the outcome measure data being appropriately and robustly analysed. However, the blinding of the outcome measures was only single blinded (i.e. assessor only) and that could introduce a source of bias that affects the interpretation of the findings. The authors further indicated that there was patient loss throughout the time period of the study that reduced from 181 at baseline to 69 patients at the 12 week and 3 month assessment points. The authors did detail the main reasons for this dramatic decrease in sample size, which included dissatisfaction with treatment allocation, inability to remain in contact with patients and medical reasons. This reduction in sample size could explain why no significant results were reported and the authors did not include an intention to treat calculation to take this into consideration. Additionally, the authors did not report exactly how they defined and confirmed that the patient had osteoarthritis of the knee joint, which is important to ensure that patients with non-OA knee conditions were not included within the sample.

In contrast, Bennell et al (2005) conducted a study to determine the efficacy of a physiotherapy programme that included an exercise component that recruited 140 participants with knee joint osteoarthritis as defined using the American College of Rheumatology, of which 119 completed the 12 week therapist led intervention and 12 week

self management period. Furthermore, this randomised, doubled-blinded and placebo controlled study included an intention to treat analysis. The physiotherapy programme included taping and massage as well as exercise therapy; whilst the placebo group received sham ultrasound and light application. The exercise therapy component of this study was defined as retraining of the quadriceps, hip and back muscles as well as balance exercise. In addition to these components, all participants allocated into this group received proprioceptive knee taping, thoracic spine mobilisation and soft tissue massage lasting a maximum of 45mins (of which includes the 10mins allocated for the mobilisation and massage interventions) once per week for four weeks and repeated fortnightly for an additional 8 weeks. The intervention was delivered by 10 different physiotherapists and the authors do not detail how they ensured standardisation of care, which could influence the results of the study. At the end of the treatment period, the participants that received physiotherapy were provided with exercises and taping instructions to complete an additional 12 weeks of self management that was monitored for patient compliance. Those patients allocated to the placebo intervention did not receive an additional 12 week self management treatment period. With regards to outcome measures used, the authors used primary outcomes of pain and patient global change, with secondary outcomes consisting of WOMAC, knee pain scale, SF-36, Quality of Life, quadriceps strength and balance. All of these measures are recognised as being reliable and valid for outcomes they are measuring. The results of the study indicated that there were no significant improvements between groups, whilst there was a slight reduction in reported pain scores ($p = 0.069$) and increases in global improvement ($p = 0.309$) in the physiotherapy group. Therefore, indicating that the physiotherapy intervention was no more effective than regular contact with a therapist. When considering that the physiotherapy intervention contained multiple components, it is possible that one or more of those components masked any potential influence that any single component could have (especially the exercise therapy component). Furthermore with the lack of reporting on how standardisation of therapy was monitored and maintained this could explain the results reported.

Similarly to the previous study that included a home based self-management programme, Chaipinyo and Karoonsupcharoen (2009) conducted a double blinded randomised study

that focused entirely on home based interventions that compared strength training to balance training in a cohort of patients with knee osteoarthritis to ascertain their impact upon on the preserving of muscle strength. However, the authors state that the primary outcome measure used within the study was pain and not muscle strength. Additionally, in contrast to the Bennell et al study, this study consisted of only 48 participants with knee OA, as defined by the American College of Rheumatology criteria, which were split equally between the two intervention groups. The study did not include any control or placebo groups to aid with comparison based analysis. The interventions were defined by the authors, which indicated that the strength training programme consisted of 30 repetitions of isometric knee extension with a 10 second maximal contraction for each leg, 5 days a week for a total of 4 weeks and the balance programme consisted of 30 repetitions of stepping and 10 repetitions bilateral mini squats repeated the same amount of times as the strength training programme. Whilst the results indicated that there were between group differences in quality of life and time to walk downstairs in favour of the strength training group, these were not significant. Additionally, for the main primary outcome measure of pain there was no significant decrease or difference between groups, however both groups did show a significant improvement in all outcomes other than knee extension strength in the unaffected knee which indicated that there may be therapeutic benefit of strength and balance exercise programmes. One area identified by the PEDro scale criteria that influences the robustness of the results that should be considered when interpreting the results of this study highlighted that there are differences between participants allocated into the groups, for example there were more males in the balance group compared to the strength group.

In 2000, Deyle et al. conducted a placebo-controlled research study to assess the therapeutic effects of exercise therapy combined with another standard of physiotherapy treatment for knee osteoarthritis, manual therapy. In contrast to previous studies, the 83 participants that were recruited onto the study were determined to have knee OA as defined by the Altman criteria that were randomised between the two experimental groups with the authors ensuring that the patient characteristics were similar in both groups. The intervention group received manual therapy determined by clinical need that consisted of

passive physiological and accessory joint movements, muscle stretching and soft tissue mobilisations that targeted the knee, lumbar spine, hip and ankle. Additionally, the authors explicitly defined the exercise therapy, which consisted of stretching, range of movement and strengthening exercises that was adjusted based upon patient tolerance. The placebo intervention comprised of sub-therapeutic ultrasound for 10mins applied to area of knee symptoms. Both groups received 30mins of total therapist delivered intervention, whilst the treatment group received additional 30-45mins to perform the exercises, twice weekly for 4 weeks. Furthermore, the participants who were allocated to the exercise treatment group performed the exercise programme on days they received no clinic based treatment at home. Therefore, there was a potentially significant difference between the two experimental groups in regards to total treatment time that may have influenced the study's results. Similar to the previous studies outlined above, one of the outcome measures utilised to determine treatment efficacy was WOMAC, pain and physical functioning as determined using the 6min walk test. In contrast to the previous papers, this study that attained a 9 out of 10 PEDro score, demonstrated a clinically and statistically significant improvement in WOMAC scores and 6min walk test at the end of the intervention and at the 4 week follow-up measurement time point for the manual therapy and exercise programme when compared to the placebo group. Therefore, suggesting that a combined physiotherapy programme does produce functional benefits in people with knee OA.

In a study, Deyle et al (2005) continued with the exploration of the clinical benefits indicated in the previous study, by comparing an exercise and manual therapy based intervention to a home based exercise program. Within this study, they utilised the same primary outcome measures (i.e. WOMAC and the 6min Walk Test), same combined intervention programme for the same length of time and used a randomised, blinded approach but without any placebo-controlled group. The home based exercise programme received verbal information sheets contained photographs of the exercises and physical demonstration of the same exercise regime as the combined intervention group that was reinforced with a clinic visit at 2 weeks. The sample size for this study was increased to 134 patients who were randomised into the two groups (i.e. combined and home based, n=66 and 68, respectively). This study that attained a 9 out of 10 PEDro score, had an extended

follow-up period of 1 year compared to their earlier study and reported that there were improvements in physical functioning at the end of treatment and the 8 week follow-up measurement, with those in the clinic based combined intervention gaining double benefit to those in the home based exercise group. Additionally, the authors reported that at the one year follow-up, both groups had substantial improvement when compared to baseline values. Therefore, this study reinforced the findings from their 2000 paper for the therapeutic benefits of combining manual therapy and exercise therapy, whilst indicating that if the exercise programme is structured and well supported can be effectively delivered and provide clinical benefit via a home based self management programme.

In a more recent publication, Doi et al. (2008) reported a similar conclusion to Deyle et al. (2005) that indicated that a home exercise programme can produce significant clinical benefits for people with knee OA. Doi et al. (2008) compared a home based exercise programme that targeted the quadriceps muscle group via knee extension movements (n=63) to Non-steroidal Anti-inflammatory Drugs (NSAIDs; n=58), used the universally accepted outcome measures of WOMAC, Japanese Knee Osteoarthritis Measure, SF-36 and Pain (i.e. VAS) and had no significant differences in patient characteristics at baseline. This randomised study demonstrated that there was an improvement in the outcome measures for both groups which was statistically significant ($p = <0.001$ for exercise group vs $p = 0.03$ for NSAID group) but it should be noted that the authors did not detail whether or not the outcome measure assessment was blinded and did not include an explicitly defined control group, which reduced its PEDro score to 7 out of 10.

Thomas et al (2005) further explored the effectiveness of home based exercise therapy for knee pain and knee OA using a pragmatic randomised controlled trial with a 2 year study duration. The study randomly allocated the 600 participants into one of four groups; (i) Exercise therapy (with Dolomite supplement), (ii) self management supported via monthly telephone contact, (iii) Exercise therapy (with Dolomite (Magnesium and Calcium)supplement) plus telephone contact and (iv) no intervention or contact but they were still required to take a prescription of a placebo herbal based medication (i.e. Dolomite). The outcomes used were WOMAC, SF-36, Hospital Anxiety and Depression

Scale (HADS) and isometric muscle strength and where administrated via a blinded assessor every 6 months. The exercise therapy programme was designed to be reflective of the individuals' condition and progression by increasing muscle resistance, whilst aiming to maintain and improve the strength of muscles that act to support the knee. However, the precise detail of the exercise therapy component was not fully described by the authors, hence it is difficult to ascertain how the objective of the exercise therapy was designed. The authors concluded that exercise decreased reported pain levels at 6, 12 and 18 months but was only statistically significant at 6 months ($p = 0.001$), especially when compared to the two non-exercise groups. Additionally, in regards to physical functioning as measured by WOMAC, exercise therapy was demonstrated to significantly increase functioning in comparison to the non-exercise groups ($p = 0.002$). Therefore, the authors concluded that exercise therapy for 30min sessions delivered daily via a home based approach can produce reductions in pain scores and can influence physical functioning. One of the strengths of the research design used in this study is the stratified randomisation based upon sex and age to ensure each group had similar patient characteristics at baseline and included power calculation to determine sample size and the analysis of results included an intention to treat basis. However, the lack of explicit details regarding the actual exercise therapy programme used makes the reproducibility of the methodology difficult.

In an earlier paper by O'Reilly et al. (1999) additional information regarding the exercise therapy protocol is provided. In this study that evaluated the effectiveness of home based exercise therapy on pain and disability (i.e. physical functioning as measured by WOMAC which was the primary outcome measure) the exercise programme that comprised of isometric quadriceps contraction held in full extension held for 20secs, and mid flexion for 5secs; isotonic quadriceps and hamstring contractions, as well as a dynamic stepping exercise is described. Each exercise component was repeated to a maximum number of 20 repetitions daily at home by those participants randomly allocated to the exercise therapy group (n=113). These participants were compared to a non-intervention group (n=78) who received no exercise based treatment intervention or any additional support of therapist visits between assessment time points. The authors reported that the exercise based group had statistically significant reductions in WOMAC pain scores ($p = 0.02$), VAS pain scores

($p = 0.03$) and WOMAC physical functioning ($p = 0.01$) when compared to the control group. One of the strengths of this study is in the sample size (n=191) which is supported by a power calculation. However, the lack of double blinding as highlighted by the authors is a possible limitation.

Previous papers that examined the effects of exercise therapy delivered via a home based approach have provided conflicting results, and McCarthy et al. (2004) designed a research study that explored the potential of supplementing the home exercise programme with an additional class based exercise programme to determine whether or not the clinical outcomes for people with knee OA would be improved. All 151 participants (as determined by a power calculation) that completed the entire 12 month trial, were included in the study if they had knee OA as defined using the American College of Rheumatology, were randomly allocated equally into either home exercise only (n=71) or class supplemented home exercise group (n=80). Regardless of which group the patient was allocated into, all participants received advice and education guidance derived from the UK Arthritis Research Campaign's publications. However, no control or placebo group was included within the research design, thus limiting the scope of the comparative statistical analysis. The exercise programme was designed to include muscle strengthening, muscular endurance (to improve fatigue levels), balance and proprioception. However, the precise details of the exercise protocol are not included in the paper, which limits the reproducibility of the methodology used but the readers are directed to the publication by Hurley and Scott (1998). Those in the supplemented exercise group received a twice weekly 45 minute group based and clinician led clinic session for a total of 8 weeks. As with previous studies included in this review, the study utilised the reliable and valid outcome measures of WOMAC and VAS pain scores but also included Aggregate Locomotor Function score, 8 metre walk test and stair ascent and descent time as well as sit to stand time. However, the lack of full blinding of outcome measures is a weakness of the research design. Conversely, one of the strengths of this paper is its inclusion of an intention to treat approach in the statistical analysis of the outcome measures. Statistically, the authors demonstrated significant improvements in locomotive functioning ($p = 0.006$) and decrease in walking related pain ($p = 0.001$) for the class supplemented exercise group.

The authors concluded that home-based exercise therapy programmes that include therapist led clinic sessions can significantly improve the clinical outcomes for people with knee OA and that this improvement remained for 12 months, when compared to only home based exercise therapy programmes.

Maurer et al. (1999) further explored the use of isokinetic quadriceps exercise therapy targeting to increase muscle strengthening and comparing its potential therapeutic effects to an intensive educational based intervention with regards knee OA related pain and physical functioning in 113 participants (which was supported by an appropriate sample size calculation). All participants recruited on the study had a confirmed diagnosis of knee OA as determined using the American College of Rheumatology criteria, at least a 3 month presence of mild to moderate knee pain and a Kellgran X-ray score of 3 or less, and were randomly allocated into either the exercise or education group. There was no control group condition that did not receive any additional interventions above normal care to aid comparative statistical analysis of treatment effects. Whilst initial clinical baseline assessments of muscle strength (as determined by isometric peak torque) were obtained for each participant under blinded assessor conditions, the authors do not state whether subsequent measures (such WOMAC, SF-36 and pain) were obtained under single-blinded conditions, which could be a source of potential experimental bias affecting the interpretation of their results. The exercise intervention received strength training of the knee extensor muscle groups, three times a week for a total of 8 weeks. During each exercise therapy session, the participants were required to complete a total of 27 repetitions separated in to three sets of extensions of 90/sec, 120/sec and 150/sec angular velocities using a dynamometer. The participants in the educational intervention group received educational leaflets, a series of 4 lectures that explored the disease process, self management, nutrition and coping strategies. The authors concluded that both interventions had statistically significant strength gains ($p = <0.001$) and demonstrated improvements in physical functioning which were not significant ($p = 0.08$). Furthermore, only participants in the exercise therapy intervention group had any improvement in pain reduction ($p = 0.007$). Whilst these results are encouraging in their support of isometric strength training improving physical functioning and pain reduction, the lack of specific

methodological detail and justifications for not including a control group or blinding processes, may influence the robustness of their findings.

In contrast to the above study, Ettinger et al. (1997) further compared exercise therapy to a structured health education program using a total sample size of 365 patients with radiographically confirmed presence of knee OA. In this study, the participants were randomly allocated into one of three groups; (i) aerobic exercise, (ii) resistance exercise or (iii) a nurse led structured health education program. The aerobic exercise group received an intervention that consisted of a small group and clinic based walking program for the first 3 months of the study, followed by a 15 month home-based walking regimen. The clinic based sessions consisted of a thrice weekly 1 hour session that incorporated a warm up period, with 40min walking at 50-70% of resting heart rate reserve (ascertained by a pre-trial treadmill test) and finished with a cool down period. Participants in the resistance (or strength training) exercise group followed the same 3 month clinic based and 15 month home based protocol. The resistance training consisted of the same warm up and cool down procedures but with an exercise protocol that contained 2 sets of 12 repetitions of 9 specific weight resisted exercises (i.e. leg extension, leg curl, step up, heel raise, chest fly, upright row, military press, biceps curl and pelvic tilt) with the objective of improving overall muscle strength and fitness. The health education programme comprised of a once monthly 1.5 hour education sessions for the first 3 months, which explored physical activity, issues related to arthritis and a social period. For the following 15 month period, these participants were supported via telephone sessions where they were encouraged to discuss their current health status and medication usage. The primary outcome measure used within the study was a self-reported measure of physical disability questions, which was generated as a result of work previously published by the research team. The secondary outcomes focused on physical performance (i.e. 6min walk test and timed activities), oxygen uptake during a treadmill test, isokinetic strength of knee flexion and extension, knee X-rays and knee pain scores (as derived from the research team's previous research). All outcome measurements were obtained with assessor blindness and repeated at regular time intervals (3, 9 and 18 months). The authors concluded that those participants that completed the aerobic exercise protocol (n=117) had significant improvements on the physical disability ($p = <0.001$) and

functioning scores ($p = 0.001$) when compared to the health education group (n=127). Additionally, the participants in the resistance exercise protocol group had significant improvements in the physical functioning ($p = 0.02$) outcomes when compared to the health education intervention but this was accompanied by a significant reduction in pain scores. Furthermore, in regards to disease progression as determined by knee X-rays, the authors demonstrated that there were no significant differences between any of the intervention groups. This randomised, controlled, single blinded clinical trial with a respectively large sample size (which was supported by a power calculation) and robust clinical outcomes provides arguably strong research evidence for the symptom management benefits of exercise therapy that would improve physical functioning levels for people with knee OA, which is reflective of its 9 out of 10 PEDro score.

However, in contrast to the above study, Rogind et al (1998) assessed the effects of a physical training programme that consisted of exercises that targeted general fitness, balance, coordination, stretching, lower limb strengthening and a daily home based programme, using only a consecutive (but random) sample of 23 patients with American College of Rheumatology defined knee OA. All participants were randomly allocated into either the exercise intervention group or control group (i.e. no intervention). The exercise intervention group consisted of a 3 month training programme delivered twice a week by a physiotherapist and comprised of well defined exercises that focused on mobility, venous therapy, lower limb muscle strength and flexibility as well as balance and coordination. The home based programme consisted of exercises familiar to the participants during the clinic based sessions and that further targeted the strengthening of the quadriceps as well as stretching the hamstrings, lower back and hip adductors. The potential long-term benefit of this intensive 3 month protocol (clinic and home based exercises) was assessed at the end of a 1 year follow-up measurement. The outcome measures used in this study were the main ones replicated in the other studies included within this review (i.e. pain and muscle strength) but the authors included a general evaluation using the Algofunctional Index, a physical clinical assessment of the knee joint and postural sway. These outcomes provide a mix of objective and subjective outcomes. The results from this study, although they could be decreased in possible robustness due to the lack of a power calculated sample size,

blinding and unequal baseline characteristics (i.e. significantly more females than males), does support previous research outlined in this review that exercise therapy may be able to significantly improve physical functioning ($p = <0.05$), increase muscle strength ($p = 0.05$) and reduce pain ($p = <0.05$) in people with knee OA.

One of the common features of the exercise programmes evaluated in the studies outlined above is the inclusion of strengthening exercises to improve physical functioning. Jan et al. (2008) explored a different aspect of examining muscle strength training for patients with knee OA, by comparing high resistance training to low resistance training in elderly subjects instead of young people, which is more reflective of the clinical knee OA population. As with most of the other papers included in this review, the confirmed diagnosis of knee OA in the patients recruited onto the study complied with the American College of Rheumatology criteria which included clinical history, presence of grade 3 bilateral radiographic changes and clinical assessment by an orthopaedic surgeon. The authors provide CONSORT (Moher at al., 2010) flow diagram to illustrate participant flow from the 133 initial contacts to the 112 participants that completed the study, which were randomly allocated into one of three experimental groups: (i) High resistance exercise(n=34), which consisted of 60% of the weight required for 1 repetition maximum (RM) repeated 8 times in three complete sets, (ii) Low resistance exercise (n=34), which comprised of 10% of 1RM repeated 15 times in three complete sets and (iii) control (n=30), which consisted of no intervention. The authors concluded that both high and low resistance muscle strengthening exercise therapies produced significant improvement for all outcome measures (i.e. WOMAC (pain and physical functioning) ($p = <0.008$), walking times ($p = <0.05$) and knee extensor and flexor torque ($p = <0.008$)). Whilst this study provides further evidence for the clinical benefit of exercise therapy that targets muscle strengthening in reducing the key characteristics of knee OA, the lack of details regarding the blinding processes included in the research design is a weakness of the study. However, this paper still attained an 8 out of 10 PEDro score.

In 2003, Huang et al. conducted a randomised trial exploring the therapeutic effects of 3 strengthening exercise (i.e. isokinetic (n=33), isotonic (n=33) and isometric (n=33))

approaches when compared to a control group (n=33). The 132 participants recruited onto the study had knee OA as defined by the Altman criteria, which had to be a bilateral presentation and all received additional home based exercise programme that comprised of 15mins cycling for the isokinetic and isotonic exercise groups and those in the isometric group were instructed to complete 30 repetitions of 5sec isometric contractions of the quadriceps and biceps femoris (hamstrings) with the knee in full extension. Muscle power of the leg at flexion and extension was the primary outcome measure, which needs to be standardised in order to increase its reliability and validity. Secondary measures included measures of physical function via VAS, ambulation speed and Lequesne Index (i.e. level of disability). The authors suggested that for all exercise therapy groups there were significant improvements in pain and disability scores as well as ambulation speed when compared to the control group (all $p = <0.05$). However, these positive results may be criticised based upon the lack of double blinding in obtaining outcome measures to ensure that the apparent effect (or lack of effect) of treatment was not due to the assessors' biases impinging on their measures of outcomes. Additionally, with the limited description of the baseline patient characteristics it is not possible to determine whether or not the research design used attempted to ensure that the groups contained similar types of patients to limit the potential bias arising by chance with random allocation. Furthermore, the sample size of the study was not explained or justified by the inclusion of a power calculation.

In a later study, Huang et al. continued the previous study utilising a similar research design in 140 patients with bilateral knee OA as classified by the Altman criteria. The experimental groups included an integrated therapy approach, whereby group 1 received the same isokinetic exercise protocol only, group 2 received isokinetic exercise combined with pulsed ultrasound designed to treat soft tissue pain (i.e. 1MHz frequency, 2.5 watts/cm^2 and a 25% pulse rate, 3 times per week for a total of 8 weeks) and group 3 received isokinetic exercise, pulsed ultrasound and intraarticular 20mg hyaluronan (an anti-inflammatory agent) injection therapy every day for 7 days for a total of 5 weeks. Outcome measures included in the study are the same as the ones used in the 2003 study. The authors concluded that an integrated therapy approach should be recommended for the effective management of knee OA, as all groups showed significant improvements in muscle peak

torque, pain and disability scores with the group 3 participants showing the greatest level of improvements between all exercise groups.

The therapeutic benefit of intra-articular hyaluranic acid injections was further compared to exercise therapy in the study completed by Karatosun et al in 2006. In this prospective non-controlled but assessor blinded clinical trial, the exercise therapy protocol used was a series of progressive, resistance based exercises that incorporated range of movement. The progressive exercise protocol included isometric exercises that targeted the quadriceps femoris muscles (week 1), stretching of the hamstrings, active range of movement, and strengthening exercises (from week 2 to 5) and proprioceptive exercises with closed kinetic chain exercises at week 6. The intra-articular hyaluranic therapy consisted of once weekly injections over a 3 week period. The authors reported that both interventions significantly improved clinical outcome in the 105 participants, (i.e. n=52 for the intra-articular hyaluranic acid therapy group and n=53 for the progressive exercise therapy group), comparing baseline to end of trial assessments as measured via the Hospital for Special Surgery Knee Score ($p = 0.0002$). However, there was no significant difference between groups indicating the exercise therapy protocol is as effective as intra-articular hyaluranic acid therapy in improving the level of physical functioning in patients with knee OA. Whilst these results are encouraging and support previously discussed papers in this review, it is important to note that this was a progressive clinical study that did not include a control group and only had assessor blinding rather than double blinding but it still achieved an 8 out of 10 PEDro score.

Whilst some of the previous papers included in this review explore the delivery of exercise therapy via small group classes, van Baar et al (2001) examined the effectiveness of exercise therapy delivered individually in patients with osteoarthritis of the hip or knee. Additionally, this single-blinded and controlled study of 201 participants (with 183 participants completing the trial) who were randomly allocated into either the exercise invention or control group provides evidence that the benefits of exercise therapy for osteoarthritis may not fully affect the patients' level of physical functioning, as the authors conclude that that any beneficial effects of exercise they demonstrated immediately post

intervention may actually decline and return to baseline values over time. The exercise protocol used in this study focused on muscle functioning (i.e. strength), mobility (i.e. physical functioning) and coordination (i.e. balance). Each exercise therapy session lasted 30min once to three times per week for a maximal total of 12 weeks, which was determined by the physiotherapist assessment of the participants' pain levels and whether or not they had received their treatment goals. In addition, the participants received further advice and guidance to support the participants' activities of daily living and they were prescribed a home based exercise regime. The primary outcomes used in this study focused upon pain scores and observed disability, which is a common feature to all studies included in this review. In contrast to other studies, the authors included a measurement of NSAIDs usage by the participant. Furthermore, the authors included a series of subjective self reported secondary outcome measures that explored global perceived effort, level of disability and level of physical activity. Whilst the findings from this study indicated that exercise therapy can produce moderate reductions in osteoarthritis related pain in the short term, these benefits are lost over time. However, it should be highlighted that whilst this study was well designed (i.e. randomised, justified sample size, single blinding, valid outcome measures etc) it did include two different clinical OA populations and this could have had impact upon the interpretation of the study's overall results.

For a summary of systematic reviews, see Table 7.

2.3.5 Rationale for Present Study

The studies evaluated appear to show a general support of the use of exercise therapy in the treatment of knee OA. The majority of papers demonstrate an improvement in pain function and strength (Ettinger 1997; Rogind 1998; Maurer 1999; Deyle 2000; Thomas 2002; Huang 2003; Deyle 2005; Huang 2005; Karatosun 2006; Doi 2008; Jan 2008; Chaipinyo 2009), with few studies reporting no statistically significant changes following exercise therapy (Bennell 2005; Williamson 2007). However, due to the wide variety of exercise methods and exercise frequency used it is difficult to draw a definite conclusion with regards to the most effective methods. The studies highlighted appear to suggest that the quadriceps and hamstring muscle groups are the most important groups to concentrate on when designing

exercise programmes to have an effect on knee OA. Furthermore, it appears that clinic-based programmes that are supplemented by home exercises appear to yield favourable results. These findings are in agreement with previous reviews carried out by Fransen (2001) and Alkhazim (2004). Common outcome measures used appear to be the WOMAC and VAS pain scales, therefore if future studies are to be designed to assess exercise intervention, these outcome measures should be used primarily to maintain continuity throughout the studies.

Future studies should concentrate on the use of clinically applicable exercises that concentrate on quadriceps and hamstring strengthening that can be delivered in the clinic and home based setting.

The following chapter will present a single blind randomised controlled pilot study that will evaluate the effect of IFT and exercise therapy in isolation and in combination. An attempt will be made to answer the null hypothesis of whether the combination of treatments leads to a greater improvement than either intervention in isolation.

Summary Table of Laboratory Based Trials

Table 5: Summary of Laboratory Based IFT Trials

Reference	n	Modality	Placebo/Control	Frequency Used	Outcome Measures Used	Effect	*p* value
Mcmanus, Ward and Robertson (2006)	20	IFT	Within-subject control	100Hz	VAS pain score and algometer and time to measure pain	Positive effect on mechanical and cold induced pain	0.017
Johnson and Tabasam (1999)	30	IFT	Placebo treatment used	100Hz	VAS pain score, self reported pain score	Positive effect on cold induced pain	<0.05
Johnson and Tabasam (2003)	21	TENS/IFT	Placebo treatment used	100Hz	Self reported pain using VAS	No significant effect found on ischaemic pain	<0.05
Jorge et al. (2006)	69 rats	IFT	Placebo treatment used	140Hz	Formalin Test and Carrageenan induced inflammation	Positive effect on inflammatory pain	<0.05

Table 6: Summary of Clinical Based IFT Trials

Reference	n	Modality	Placebo/ Control	Frequency Used	Outcome Measures Used	Effect	*p* value
Cheing and Chan (2002)	62	TENS	Placebo treatment	80Hz	VAS	Positive effect found on knee pain in TENS group	<0.001
Cheing and Chan (2004)	66	TENS	Placebo treatment	80Hz	Peak torque, gait parameters, ROM	Positive effect found on all parameters when TENS combined with exercise	0.053
Hurley et al. (2004)	240	IFT	None	140Hz	Roland Morris Disability Questionnaire, Mcgill pain questionnaire, SF-36	Positive effect on disability and pain in acute low back pain	0.036
Walker et al. (2006)	9	IFT	None	100/10Hz	VAS for pain and morning stiffness, SF-36	Positive effect found on SF-36 body pain, morning stiffness but no effect found on patient assessed pain in psoriatic arthritis	0.02
Jarit et al. (2003)	87	IFT	Placebo treatment used	5-10/ 80-150Hz	Oedema, ROM, Pain and pain medication	Positive effect found on all outcome measurements in post-op knee patients	N\A
Adedoyin et al. (2002)	30	IFT	Placebo	100/80Hz	10-point pain scale	Positive effect found on pain in patients with knee pain	N\A
Adedoyin et al. (2005)	46	IFT	None	80Hz	WOMAC scale, 10-point pain scale	Positive effect on pain and function in knee OA when combined with exercise	0.001

Table 7: Summary of Exercise Therapy Trials

Reference	No. of subjects	Exercise compared with	Type of exercise used	Outcome measures used	Effect of exercise therapy	Directional Change	p-value
Huang et al. (2005)	140	Ultrasound Hyaluronic Acid	Kin-Kom Isokinetic	Lequesne Index ROM, peak muscle torque, ambulation speed, VAS	Significant reduction in pain, disability. Significant increase in ROM	Improvement in favour of exercise group	<0.05
Huang et al. (2003)	132	Isometric, Isokinetic and Isotonic exercise	Kin-Kom	Muscle strength, VAS, ambulation speed, Lequesne Index	All groups showed significant improvements, with isotonic showing greatest increase	Improvement in all exercise groups	<0.05
Van Baar et al. (2001)	201	Normal GP treatment, i.e education, medication	Individual exercises given in class and at home	Pain Drug Use Observed Disability	Small improvement in pain at 24 weeks, no effect at 36 weeks	No overall change	>0.05
McCarthy et al. (2004)	214	Home exercises compared with addition of class-based exercise	Muscle strengthening, proprioception and balance exercises	ALF score 8-metre walk time Stair ascent and descent time VAS WOMAC	Significant improvement in both groups, although class based exercise group showed greater improvement at 12 months	Improvement in all exercise groups	<0.001 (ALF) <0.001 (VAS) 0.003 (WOMAC)
Ettinger et al. (1997)	439	Aerobic and Resistance exercises compared to health education	Walking programme Kin-Kom Isokinetic	Self Disability Treadmill Test Strength Pain X-Ray	Both exercise groups showed significant improvement in Disability, pain and strength. There was no change in X-ray in any group	Improvement in all exercise groups	<0.05
Rogind et al. (1998)	25	Comparison made to control group	General stretching and strengthening exercises including home exercises	Muscle Strength Functional Index Pain Walking speed	Significant improvement in functional index and walking speed	Improvement in favour of exercise group	<0.05

Jan et al. (2008)	102	High and low resistance training compared to control	Cycling and individual programmes	Pain WOMAC Walking time Knee flexion/extension torque	Significant improvement in all exercise groups in all interventions. Slightly greater improvement in high-resistance group	Improvement in all exercise groups	0.008 (WOMAC) <0.05 (Walking time) <0.008 (Torque)
Karatosun et al. (2006)	200 knees (105 patients)	Progressive exercises compared to hyaluranic acid	Progressive ROM and resistance exercises	HSS Knee score	Statistical improvement in both groups. No differences between groups	No improvement in one group over the other	<0.01
Deyle et al. (2005)	134	Home exercises compared to clinic exercises and manual therapy	Cycling ROM exercises Strengthening exercises	6-minute walk WOMAC	Significant improvements in both outcome measures in both groups. Greater improvement in clinic based group	Improvement in exercise group	<0.04
Thomas et al. (2002)	786	Exercise therapy compared to telephone contact or no treatment	Muscle Strengthening, ROM maintenance	WOMAC (Pain) SF-36 (function) Strength	Exercise therapy demonstrated significant reduction in pain No change in SF-36. Significant improvement in strength	Improvement in favour of exercise group	0.001 (Pain) 0.002 (Strength)
Williamson et al. (2007)	181	Exercise Therapy (Physiotherapy) compared to acupuncture and advice	Circuit based exercises addressing quadriceps weakness and function	Oxford Knee Score WOMAC VAS Hospital Anxiety Score	At 12 weeks there was no significant difference between groups	No overall change	>0.05
Chaipinyo et al. (2009)	48	Home based strength training compared to home based balance training	Strength group performed static quadriceps strengthening and balance group performed balance exercises	Knee Injury and OA outcome score Strength	No between group differences Significant improvement in both groups in all outcomes	Improvement in all exercise groups	<0.05

Bennell et al. (2005)	140	Physiotherapy including exercise compared against placebo ultrasound	Home exercises aimed at a number of muscle groups	VAS WOMAC SF-36 Quality of life score	Both groups reported non-significant reduction in pain Physiotherapy improved quality of life significantly	Improvement in favour of exercise group	0.069 (Pain) <0.05 (Quality of life)
Maurer at al. (1999)	113	Isokinetic exercise compared against Education	Kin-Kom Isokinetic exercises	Strength Pain WOMAC	Both groups produced significant strength gains and improved WOMAC scores. Only the exercise group saw significant reduction in pain	Improvement in favour of exercise group	<0.001 (Strength) <0.05 (WOMAC) <0.001 (Pain)
Doi et al. (2008)	142	Home based exercise compared with Non-steroidal anti-inflammatory drugs	Quadriceps strengthening exercises	WOMAC SF-36 VAS	All outcomes improved significantly in the exercise and NSAID group with no significant difference between groups	No difference between groups	<0.001
Deyle et al. (2000)	83	Home based exercise and manual therapy compared with placebo ultrasound	Muscle strengthening and ROM exercises to hip and knee	WOMAC 6-minute walk	Exercise group performed significantly better than placebo in both outcomes	Improvement in favour of exercise group	<0.05
O'Reilly et al. (1999)	191	Strengthening exercises compared to no treatment	Quadriceps strengthening exercises	WOMAC VAS Strength	Exercise group performed significantly better in all outcomes	Improvement in favour of exercise group	<0.05

3.0 Clinical Trial: Assessing the effect of IFT and Exercise Therapy on KneeOsteoarthritis: A Pilot Study

3.1 Summary

BACKGROUND:

Osteo-Arthritis (OA) is one of the most prevalent diseases that affects the major joints of the musculoskeletal system. Osteo-Arthritis of the knee is particularly disabling due to symptoms such as pain, stiffness and muscle weakness (Mcalindon et al. 1992, O'Reilly et al. 1998). One aspect of the care of people living with Osteo-Arthritis of the knee involves the referral to a physiotherapist for symptom management. The mainstay of physiotherapeutic intervention is exercise therapy targeting the muscles that surround the knee to improve function. One modality also used to address pain felt during exacerbations of OA is Interferential Therapy (IFT).

OBJECTIVE:

The Objective of this MPhil study was to explore the current concepts and research base surrounding the use of exercise therapy and IFT in the treatment of OA knee and to compare the effects of the two different treatment methods on OA of the knee, and to ascertain whether the effects of the modalities are increased when used together.

METHODS:

36 subjects suffering with OA of the knee were randomly split into 3 groups. Group 1 received Exercise Therapy treatment only. Group 2 received Interferential Therapy only. Group 3 received both treatments. All subjects acted as their own control. Outcome measures used were VAS pain scale, WOMAC, and ROM using goniometer.

RESULTS:

Changes in the combination treatment group were found to be most significant of the treatments used. Significant improvements were found in the exercise therapy group on all outcome measures. Interferential Therapy did not produce any significant changes when used in isolation.

CONCLUSION:

Combination treatment is clinically effective for the treatment of Osteo-Arthritis of the knee, however exercise therapy in isolation is also an effective and suitable treatment. More studies need to be carried out to evaluate the most effective settings to be used in the treatment of Osteo-Arthritis of the knee when using Interferential Therapy, and to assess the true financial implication of using combination treatments.

3.2 Introduction

Knee OA is a common pathology in the western world (Sisto 2006). It becomes increasingly common as the population ages and can become a burden to the sufferer leading to worsening physical function and disability (Peat 2001). It is thought that as many as 10% of people over the age of 65 in the US suffer with the disease (Felson, 1982) leading to an economical cost of around $86 billion (Abell 2005). Therefore the best ways to manage the condition are important to keep the physical functioning of the individual sufferer high and the cost to the economy low.

Previous chapters have commented on research that has looked the effect of exercise therapy and IFT on OA of the knee in isolation. This work has demonstrated positive results and suggested that the use of both modalities could be useful in addressing the muscle weakness, reduced function and pain that usually affects the OA knee sufferer. However, few studies have looked at the effect of both modalities in combination and it could be hypothesized that the use of both modalities may lead to a greater overall treatment effect than either intervention alone.

This pilot study plans to look at the effects of each intervention in isolation and in combination to assess the effect of both IFT and exercise therapy on OA knee in the clinical environment. The study plans to produce data that may be used to plan a larger scale study to more accurately assess the effect of the combination of treatment techniques to treat OA knee in the future.

3.3 Methodology

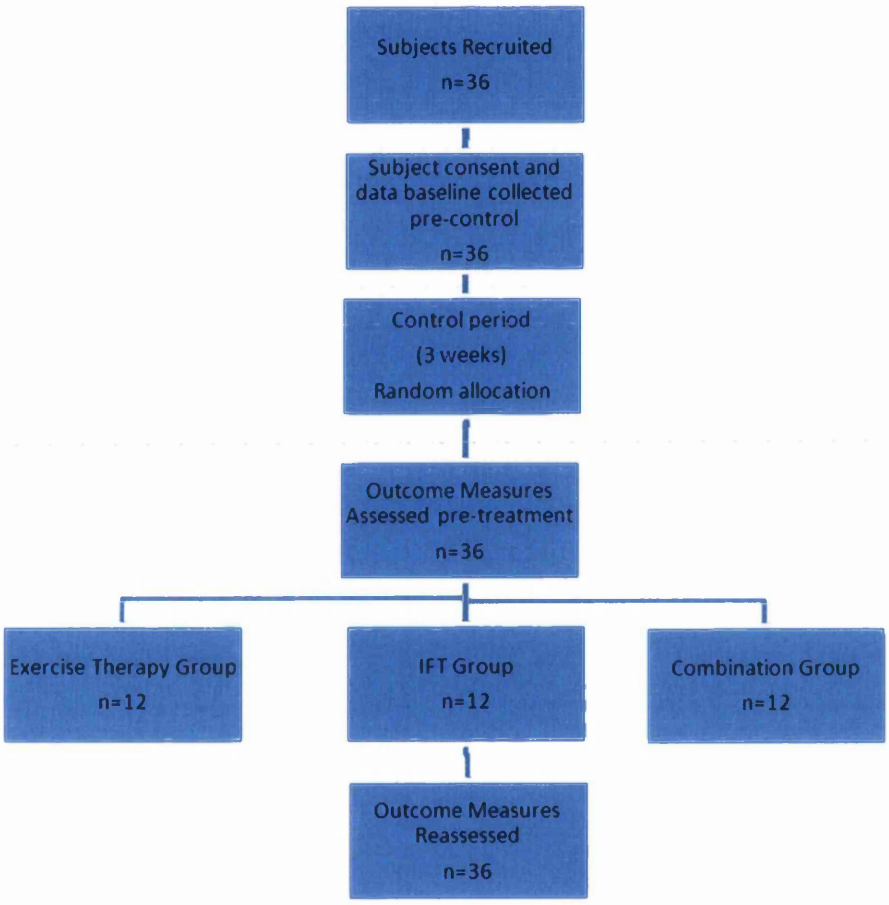
3.3.1 Study Design

As was seen in the previous review chapter, the methods of clinical design differ quite considerably, however, based on the majority of the studies reviewed, and guidance following ethics review, the present pilot study was designed. The aim of the present pilot study was to test the trial design to guide a future larger scale study.

Following guidance from the ethics review panel, it was decided that a single blind randomized controlled trial would be the most efficient way to carry out the study. The novel method of having subjects act as their own control would avoid any symptomatic subjects receiving no treatment, yet still enable comparison of the same subject following a period of no treatment. Ideally, the design would have been double blinded but subjects were required to be made aware of the various treatment options and therefore, the blinding of the subjects to their treatment group would have been unrealistic. One of the main researchers (Craig Dyson) was used to deliver the treatment in that phase of the study, and it could be justifiably questioned as to whether the involvement of one of the main researchers in treatment delivery could impart an element of bias, however due to financial restraints it was decided to involve him in this stage of the study and have a blinded member of staff (Ron van Heeswijk) carry out the data collection and assessment of subjects pre-control, pre-treatment and post-treatment. The staff member that was used to take measurements had over 20 years experience and was tested for reliability in taking measurements according to a protocol using consistent anatomical landmarks for ROM using the goniometer.

Randomised controlled studies are used to test an association between an intervention and an outcome, with the effort made to randomize subjects ruling out any confounding differences in the groups (Sibbald and Roland, 1998). The present pilot study tested subjects over a period of six weeks in total with no follow-up period. This was done due to financial constraint as ideally subjects would have been followed up for a longer period. Subjects were treated over six sessions as this was the average number of treatments in the clinical setting based on the clinical experience of the author, however following review of previous studies, had finances allowed, up to 12 treatments could have been considered. Outcomes used were WOMAC (Bellamy, 1982), NRS for pain and joint ROM measuring flexion. These outcomes were used as WOMAC (Bellamy, 1982) is a commonly used outcome when assessing this type of condition according to previous studies reviewed in earlier chapters. NRS for pain and joint ROM are also commonly used in clinical departments, and this was the main factor in their use in the present study.

Flow Chart 5: Study Design



3.3.2 Subjects

Thirty-six subjects, aged 45-70 years old all suffering with knee OA were recruited from specialist GP, physiotherapy and consultant clinics around Abertawe Bro-Morgannwg University NHS Trust. Subjects were referred into these clinics by their GP.

3.3.3 Inclusion Criteria

Inclusion Criteria were as follows:

1. Age 45-70 years
2. Confirmed osteo-arthritis (OA) of the knee by way of radiological investigation (X-Ray).
3. Osteo-arthritis as defined by Altman (1986), i.e. the patient experiences pain and any five of the following:

1. Over 50 years of age,
2. Less than 30 minutes of morning stiffness,
3. Crepitus (noisy, grating sound) on active motion,
4. Bony tenderness,
5. Bony enlargement,
6. No palpable warmth of synovium,
7. Erythrocyte sedimentation rate (ESR) less than 40 mm/hr,
8. Rheumatoid factor less than 1:40 titer (agglutination method),
9. Synovial fluid signs.

3.3.4 Exclusion Criteria

Patients were excluded from the study if they:

1. Had had any other treatment in the previous six weeks
2. Had any other medical condition which could explain their current complaints.
3. Kellgren Grade IV OA (large osteophytes (bony growths), marked joint space narrowing, severe sclerosis (hardening of the cartilage) and definite deformity of bone ends. This is applied when X-Ray shows a very high level of OA presence)(Kellgren 1957).
4. Were suffering with patello-femoral joint OA (Osteo-arthritis of another joint)
5. Were contra-indicated for exercise treatment or Interferential Treatment (IFT)

Contraindications for IFT are as follows:

- Subjects whose skin is easily damaged or bruised
- Subjects who are on anti-coagulation therapy
- Subjects with pacemakers,
- Subjects who have active malignancy.

Contraindications to exercise therapy are as follows:

- Any uncontrolled cardiac conditions (aortic stenosis,cardiac enlargement,dysrhythmias,ventricular aneurysm,cardiomyopathy,congestive heart failure)
- Any uncontrolled metabolic disorders (Diabetes, thyrotoxicosis, myxedema).

6. Are unable to read and understand English.

3.3.5 Procedure

Subjects were assessed for their suitability for the study in the specialist clinic and if suitable, were given an information sheet about the study. The information sheet (Appendix2) contained details of the investigation and stated that subjects had the right to withdraw from the study at any time. The information sheet also contained the contact details of the Chief Investigator (Craig Dyson). Subjects were instructed to contact the Chief investigator if they wished to be included in the study. On contact with the Chief Investigator, subject name and contact details were taken, and allocated to a subject number and then an appointment was made to meet a physiotherapist (Ron van Heeswijk) who acted as the assessor of subject outcomes. The physiotherapist was blinded to the subject treatment. Informed consent was obtained via a consent form (See Appendix 3) issued prior to the start of the data collection process by the blinded physiotherapist. The blinded physiotherapist carried out the following outcome measures during the initial assessment:

1. WOMAC Scale which consists of 24 questions, each corresponding to a visual analogue scale, designed to measure subjects perceptions' of pain, stiffness and dysfunction. This has been shown to be a valid and reliable measure of function in patients with orthopaedic problems (Bellamy et. al, 1988; Bellamy et al., 1988). The WOMAC scale is a rating of function that uses a participants rating of difficulty of a number of functional tasks on a scale of 0 (No pain) to 5 (Unable to do). Therefore, a higher score indicates worsening functional ability.
2. Numerical Rating Scale (NRS) pain score. This is a numerical rating scale between 0-10. The subject is asked to rate their current pain on a scale of 0-10 with 0 meaning no pain and 10 meaning the worst pain imaginable. This has been shown to be a valid measure of changes in chronic pain (Price et al., 1983)
3. Range of Movement. This will be a measurement of the subjects knee flexion and extension by the blinded physiotherapist. This will be measured using a standard AMS protractor goniometer. It was decided to use this type of goniometer as this type of equipment is low-cost and commonly used in physiotherapy departments in the UK.

Measurements were taken with the subject in supine, using lateral joint line of the knee as the fulcrum point, and the femur and fibula as the other points of reference.

Following collection of the data, subjects were given another appointment three weeks following the initial assessment. This three week period acted as the control period. After three weeks, subjects were again assessed by the blinded physiotherapist using the same outcome measures, and were commenced on the treatment procedure to which they were randomly allocated.

Subjects were randomly allocated into one of three intervention groups:

1. Interferential Therapy only group
2. Exercise Therapy only Group
3. Combined therapy group

3.3.5.1 IFT Group

Subjects in the IFT group received IFT twice a week, for three weeks, i.e. six sessions in total. Each session lasted for twenty-five minutes and IFT was concentrated on the symptomatic knee. Standardized IFT stimulation parameters for pain relief were used: carrier frequency 3.85kHz; 80-120Hz sweep; pulse duration 130μs. Four electrodes were placed around the knee joint so as to concentrate the effect of the IFT into the centre of the joint and were attached via a velcro strap to ensure maximum skin contact.
IFT was administered by the chief investigator.

3.3.5.2 Exercise Therapy Group

Subjects in the exercise therapy group were treated twice a week for twenty minutes. The session was broken up into the following format:

1. Warm up using static exercise bike x 3min at slow pace.
2. 6 exercise stations. Subjects exercised at each station for 40sec with 20 sec for change of station. Subjects completed the circuit 3 times.
3. Warm down using static bike x 3min at slow pace

For example, each subject did a warm up followed by the following circuit three times. After doing the circuit three times the subjects did the warm down.

Participants did the following commonly used exercises:

1. Inner Range Quads in long sitting (sitting with legs on plinth and contracting quads muscle).
2. Single Leg Balance. (Balancing on one leg)
3. Straight Leg Raise (sitting with legs on plinth and, keeping the leg straight, lifting the leg 2-3" off the bed).
4. Step Up Exercise (stepping up onto a step)
5. Passive Knee Flexion (the participant pulls their knee into a bent position)
6. Hamstring Curl (the participant lies on their front and bends their knee against gravity).

Exercises used primarily target the quadriceps and hamstrings muscle groups as suggested in previous trials reviewed (see Section 2.3.5). Subjects in the exercise group were supervised by the chief investigator. Subjects were encouraged to continue with the exercises at home, but, in keeping with clinical practice, this was not supervised.

3.3.5.3 Combined Group

Subjects in the IFT and Exercise group did the above exercise regime and then received 25 minutes of IFT set at the above parameters.

3.3.5.4 Control Group

Subjects acted as their own control as they were assessed following initial recruitment, then they waited three weeks to simulate a control period, with a further assessment again prior to starting the treatment. Any subjects that complained of increased symptoms following an exercise period, their exercise protocol were modified accordingly on the opinion of the supervising physiotherapist.
Following completion of the study, subjects were offered conventional physiotherapy.
The second set of outcome measures were recorded at least 48 hours after the last set of exercises to allow for any post-exercise stiffness to dissipate.

Subjects were advised to continue using any medication prescribed prior to the start of the study, but were excluded if any changes in analgesic medication occurred during the study. Subject name and contact details were allocated to a reference number on allocation to the study. This data was stored on password controlled university computers at Swansea University. This data was only be accessed by the Chief investigator and the research team. All assessment data recorded during the study was kept in a sealed container in a lockable cabinet in Singleton Hospital. This was be accessed by the blinded physiotherapist carrying out the assessment, and the Chief investigator. Following completion of the study, all data will be stored at Swansea University for 10 years in compliance with the Data Protection Act 1998.

3.3.6 Data Analysis

Normality tests were carried out on patient demographics using the Shapiro-Wilks test (Shapiro and Wilk, 1965). Height, weight and time since diagnosis was all proved to be normal and therefore, further analysis was done using the ANOVA test.
Outcomes measured were function, using the WOMAC scale (Bellamy, 1982), pain using the NRS, and ROM of the knee joint. Shapiro-Wilks proved the data on pain and extension ROM to be not normal. WOMAC data is measured on a likert scale, thus non-parametric tests were used for further analysis and flexion ROM was proved to be normal and

therefore ANOVA tests were used for further analysis. Data proved to be not normal was analysed using the Kruskal-Wallis test (Kruskal and Wallis, 1952).

3.3.7 Ethics

Ethical approval for the study has been granted by the South West Wales Research Ethics Committee. Please refer to appendix 4 for a copy of the application and confirmation letter.

3.4 Results

3.5 Patient Demographics

Table 8: Patient Demographics

Group	n	Time since Diagnosis (Months)	Gender Male	Female	Height (Inches) mean±sem	Weight (lbs) mean±sem	BMI
All	36	9.36	14	22	65.79 ± 0.8	181.86 ± 7.33	29.2
IFT Only	12	9.67	5	7	66.33 ± 0.99	177.89 ± 7.86	28.7
Exercise Therapy only	12	10.83	5	7	66.2 ± 1.55	199.4 ± 16.03	32.1
Combination Group	12	7.58	4	8	64.78 ± 1.62	166.33 ± 10.33	27.7

Subject demographics are outlined above. Thirty-six subjects were included in the study. Time since diagnosis details were obtained from date of diagnostic study (X-ray, MRI) until date of starting intervention process. Height and weight details were obtained for twenty-eight subjects as eight subjects did not reply to questionnaires. BMI was calculated according to average height and weight values for the group.

Mean time since diagnosis for subjects within the study was 9.37±1.83 months (mean ±

S.E.M.). Therefore, on average, subjects were referred to physiotherapy from specialist care within 9-10 months.

The study group was made up of fourteen male subjects and twenty-two female subjects. Average height within the group was 65.79 inches (5'6") and the average weight was 181.86lbs (12 stone and 13lbs). This gave an average Body Mass Index (BMI) of 29.2 which is classed as overweight in the BMI categorising system.

3.5.1 Between Group Demographics

Exercise Therapy Group

The exercise therapy group contained five male subjects and seven female subjects. Average time since diagnosis was 10.82 months. Average height for patients within the exercise therapy group was 66.2 inches (5'6") and average weight was 199.4lbs (14 stone 3lbs), giving an average group BMI of 32.1, which is classed as obese on the BMI classification system.

Interferential Therapy Group

The IFT group contained five male subjects and seven female subjects. Average time since diagnosis was 9.67 months. Average height for patients within the IFT group was 66.3 inches (5'6") and average weight was 177.89lbs (12 stone 9.9lbs), giving an average group BMI of 28.7, which is classed as overweight on the BMI classification system.

Combination Group

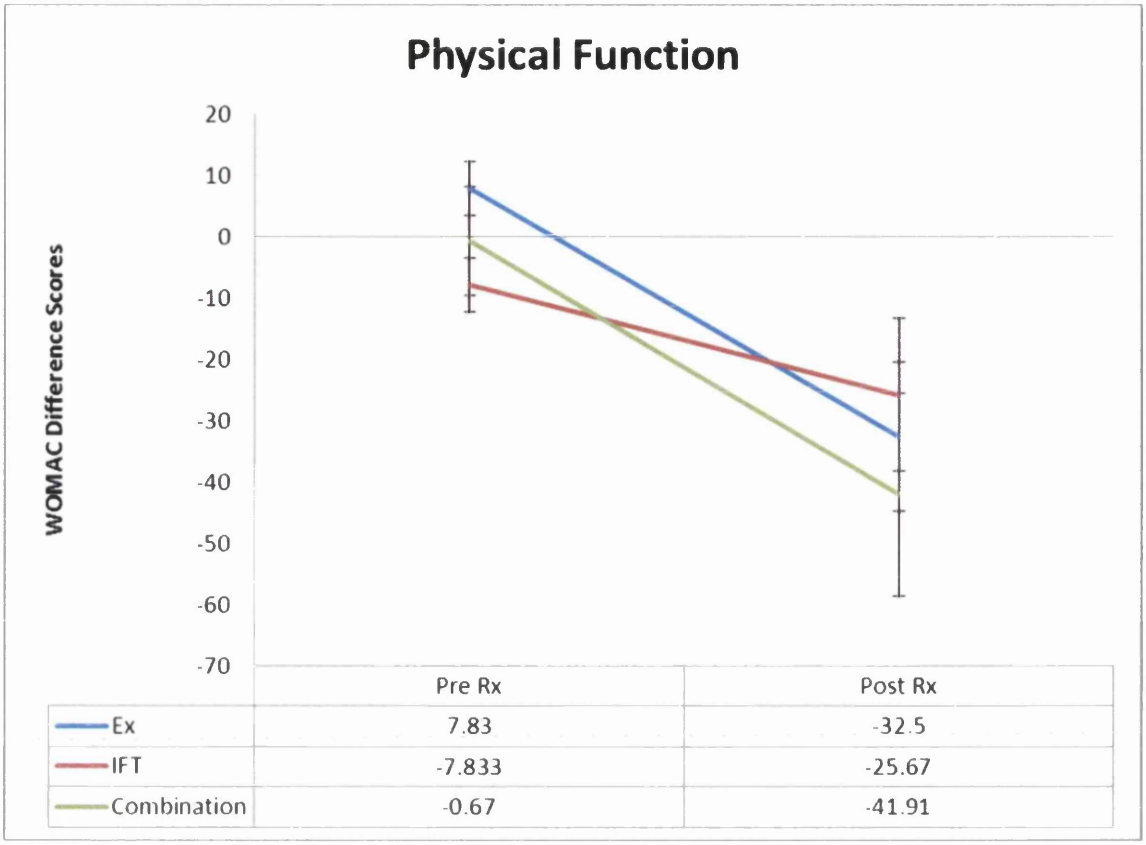
The combination group contained four male subjects and eight female subjects. Average time since diagnosis was 7.58 months. Average height for patients within the combination group was 64.78 inches (5'5") and average weight was 166.33lbs (11 stone 12.3lbs), giving an average group BMI of 27.7, which is classed as overweight on the BMI classification system.

Analysis of between group demographics

Data collected from each group for height, weight and time since diagnosis were each tested for normality using the Shapiro-Wilks test (Shapiro and Wilk, 1965). These tests proved the data to be normal and thus between group tests were done using the ANOVA test. Following these tests it was proved that there were no significant differences between groups for height (p=0.861), weight (p=0.164) or for time since diagnosis (p=0.773) at baseline.

3.6 WOMAC

The primary outcome measure used in the study was the The Western Ontario and Mcmaster Universities Arthritis Index (WOMAC).



Graph 1. Changes in WOMAC score during the intervention period across all groups.

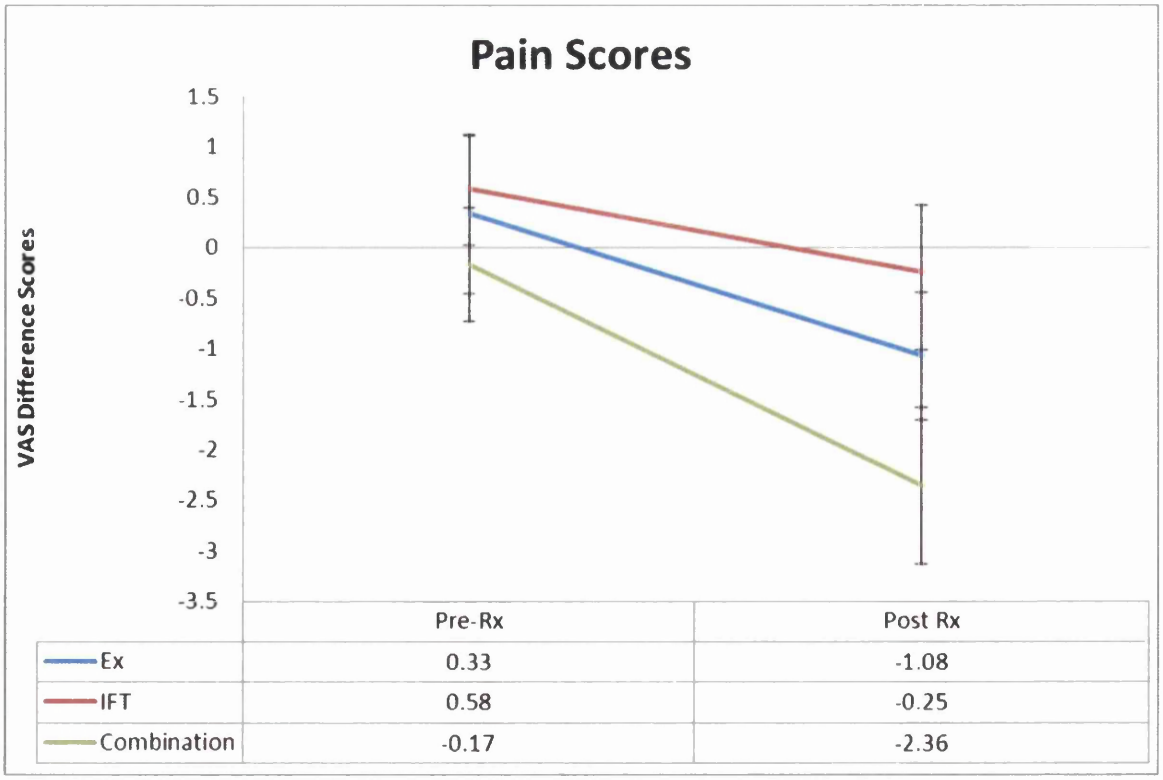
The graph above outlines the changes of WOMAC scores in subjects in each of the three different treatment groups. Subjects measurements were taken at baseline prior to control period (0 weeks), prior to intervention (3 weeks), and after the intervention period (6 weeks). The graph shows that over the initial period, the exercise therapy group appears to deteriorate in terms of WOMAC score over the control period, thus increasing WOMAC scores by 7.83 ± 4.83 SEM, as opposed to the other two groups which appear to improve slightly, decreasing the score in the IFT group by 7.83 ± 4.31 SEM and in the combination group by 0.67 ± 8.85 SEM. Every group appeared to improve over the second three week period. The exercise (32.5 ± 12.1 SEM) and combination group (41.91 ± 16.53) show greatest improvement over the intervention period, whereas the IFT seems to show a relatively constant improvement from the initial baseline to post intervention (25.67 ± 12.46 SEM).

The WOMAC scale is scored using a Likert scale and therefore is not interval/ratio data. As a result, the Kruskal Wallis (Kruskal and Wallis, 1952) test was used to analyse data. Analysis showed that there was no significant improvement between groups at any point during the study.

However, when testing within group differences, significant changes were identified. To compare within group differences a Wilcoxon Signed Ranked test was used. The exercise therapy group improved significantly over the 0-6 week period (p=0.034), and over the 3-6 week intervention period (p=0.01). The IFT group showed no significant within group improvement over any period, however the combination group demonstrated a significant improvement over the 0-6 week period (p=0.041) and over the 3-6 week intervention period (p=0.026).

3.7 Pain

Pain was assessed using a 10-point pain scale ranging from no pain at all to worst pain imaginable.



	Pre-Rx	Post Rx
Ex	0.33	-1.08
IFT	0.58	-0.25
Combination	-0.17	-2.36

Graph 2. Changes in pain over the intervention period across all groups

The graph above outlines the changes in pain in subjects throughout the study. Over the control period, pain appears to increase in both the exercise (increase of 0.33 ± 0.79 SEM) and IFT groups (increase of 0.58 ± 0.53 SEM). However, over the same period pain in the combination group appears to decrease (0.17 ± 0.56 SEM). During the intervention period, every group appears to improve in terms of pain, leading to an overall decrease in every group in terms of pain. The exercise group improved by 1.41 ± 0.63 SEM, the IFT group by 0.83 ± 0.66 SEM, and the combination group by 2.53 ± 0.77 SEM.

On statistical testing, initial tests using the Shapiro-Wilks test (Shapiro and Wilk, 1965) proved the data to be not normal and therefore, the Kruskal-Wallis (Kruskal and Wallis, 1952) test was used to analyse the data. There was a significant difference demonstrated between the IFT and combination groups in terms of pain over the 6 week period using the post-hoc Kruskal-Wallis test ($p=0.05$).

Within group tests were carried out using the Wilcoxon Signed Ranked test. Only the exercise therapy group demonstrated a significant decrease over the intervention period ($p=0.021$; Pre-treatment 0.33 ± 0.79 SEM vs post-treatment -1.08 ± 0.63 SEM). Although the other groups appear to show a positive trend, this was the only demonstrable significant improvement within groups for pain.

3.8 Range of Motion

Range of motion at the knee joint was measured using a standard AMS protractor goniometer following the procedure described in section 3.3.5. Flexion and extension at the knee was measured.

3.8.1 Reliability Analysis for Errors in Range of Movement (ROM) Measurement

To examine the level of agreement, magnitude and reliability of the ROM measurement of knee flexion and extension; the measures obtained at the start of the trial (i.e. initial assessment at the start of the control period) and pre-intervention (i.e. the end of the control period) were analyzed using correlational analysis and Spearmans Rho (Spearman, 1904). These tests explored the level of relationship between the measures at the two time points. Additionally, a Bland Altman Plot was generated to determine the level of agreement within 95% Confidence Intervals (i.e. 2 standard deviations).

The table 9 below summarises the findings from a number of approaches to assess the level of error in measurement and how this relates to reliability and levels of agreement in obtaining that measurement relating to range of movement.

Table 9: Level of Agreement between Range of Movement Scores for initial and pre-treatment measures (i.e. control period)

Outcome	Correlation	Spearmans Rho
Flexion	r=0.78 (p<0.00)	r=0.75 (p<0.00)
Extension	r=0.36 (p=0.03)	r=0.38 (p=0.03)

A Bland Altman plot analysis was conducted to explore the level of agreement for the 2 measures of flexion and extension range of movements; this is illustrated in Figures 2 and 3 below, with a summary of the data used in the plots in table 10.

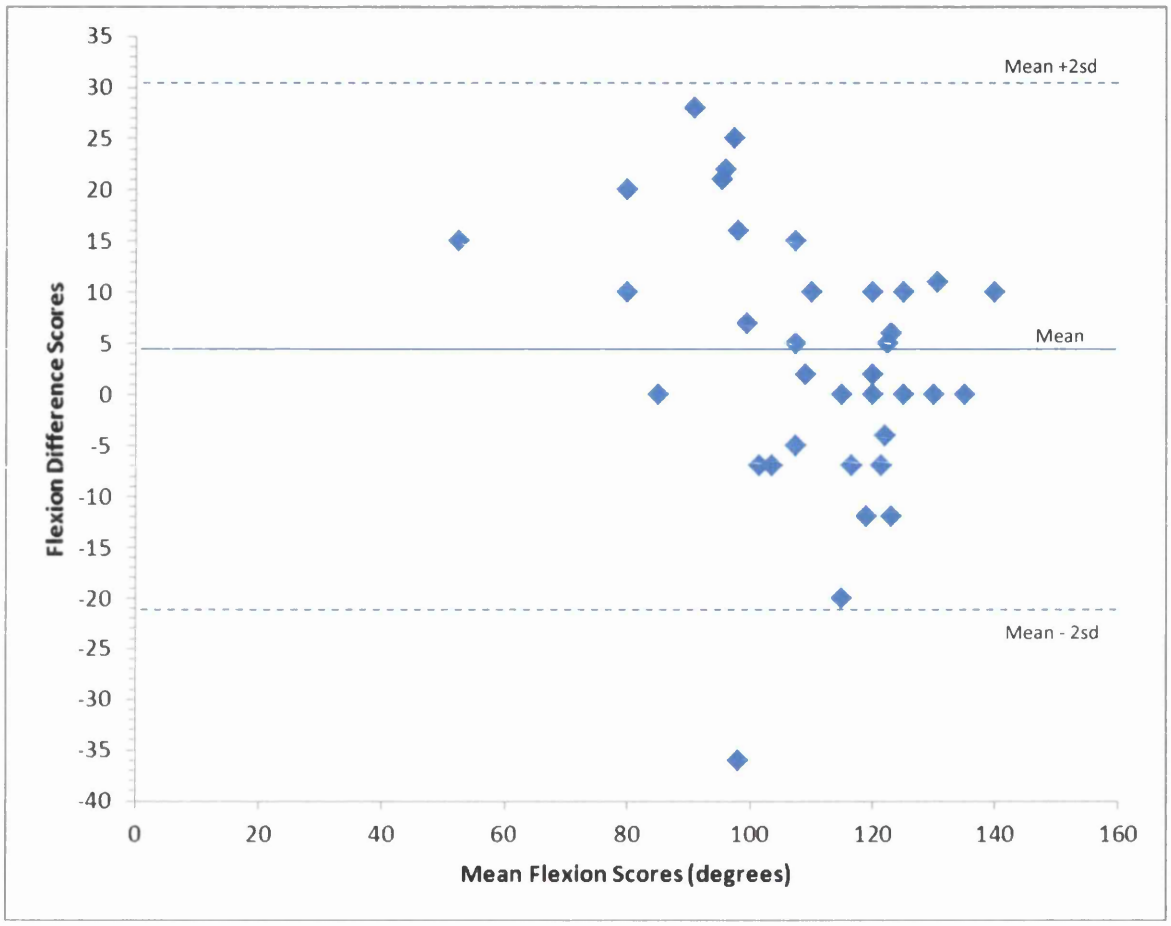


Figure 2: Bland Altman plot for flexion difference scores versus mean flexion scores to demonstrate the clustering of values between 2 standard deviations.

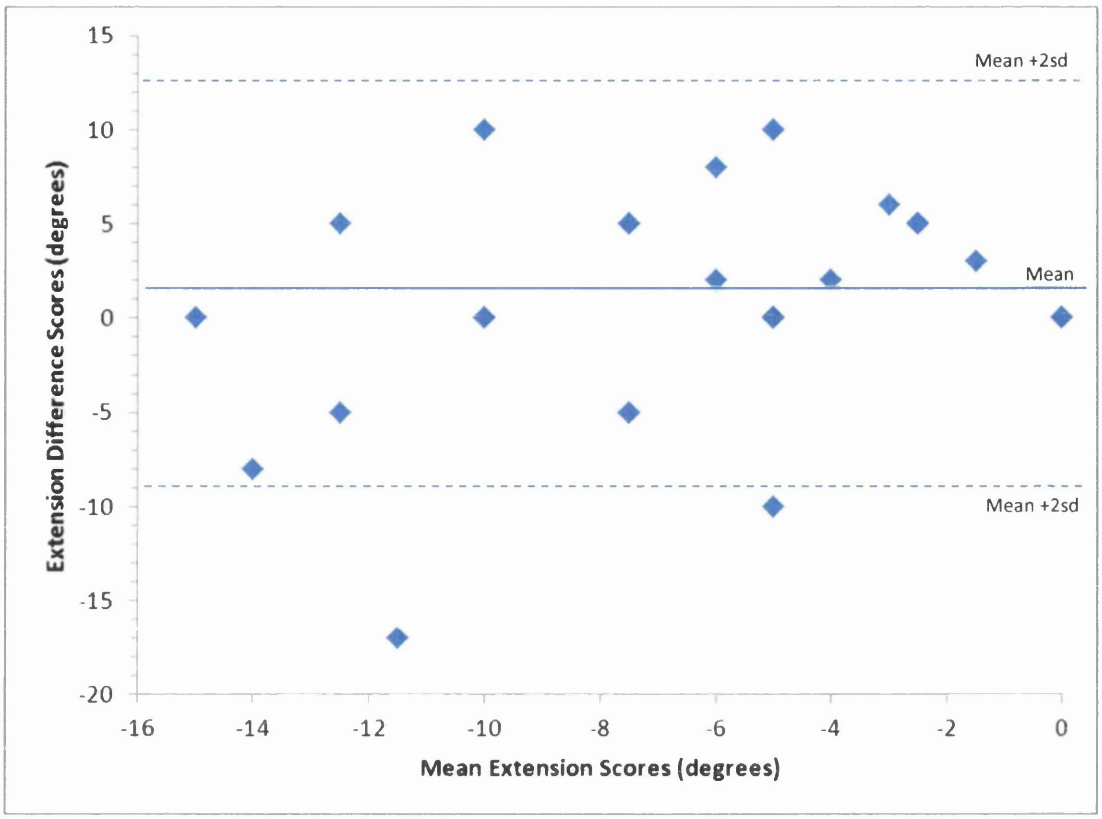


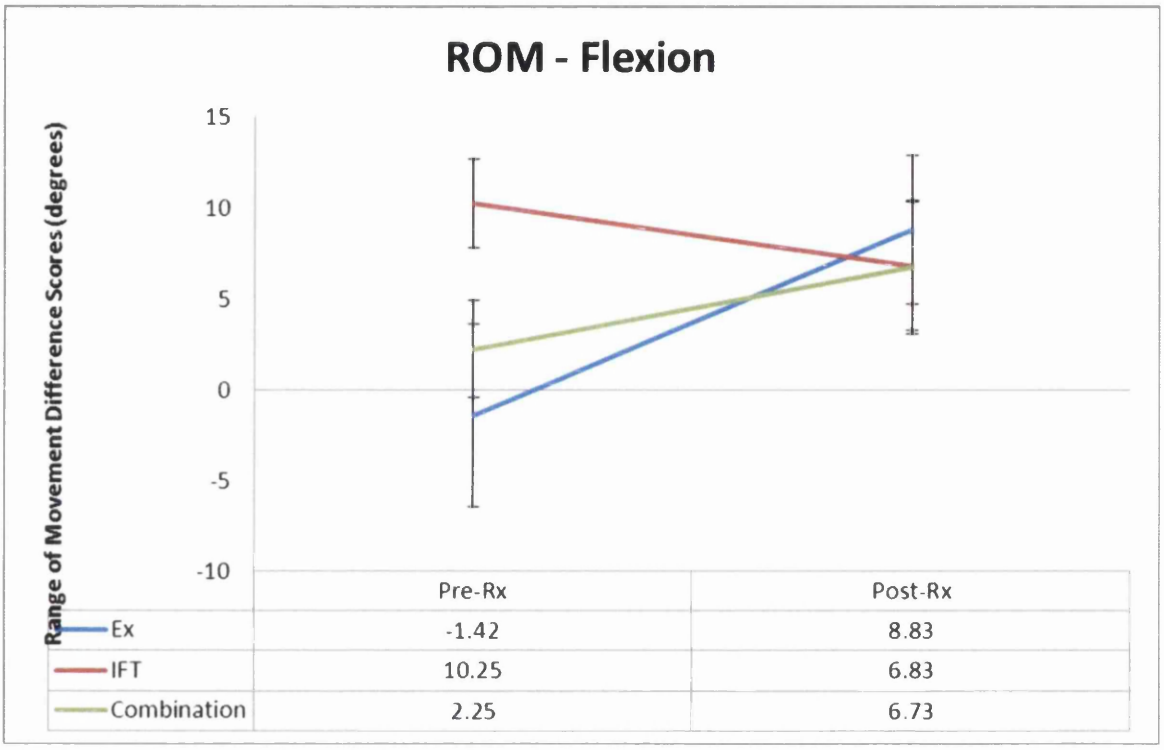
Figure 3: Bland Altman plot for extension difference scores versus mean extension scores to demonstrate the clustering of values between 2 standard deviations.

Table 10: Bland Altman summary data table.

Outcome	Mean Difference Score	Difference Score Standard Deviation (sd)	Sd x 2	Mean + 2sd	Mean – 2sd	Percentage of scores within ±2sd
Flexion	3.7	13.02	26.04	30.01	-22.34	97.3%
Extension	1.27	5.63	11.26	12.53	-9.99	94.5%

The figures and tables above demonstrate that measurements of flexion and extension of the knee fall within 95% confidence interval limits, thus demonstrating a high level of agreement between measures and therefore a high level of reliability.

Flexion



	Pre-Rx	Post-Rx
Ex	-1.42	8.83
IFT	10.25	6.83
Combination	2.25	6.73

Graph 3. Changes in knee flexion during the intervention period across all groups

The graph above shows changes in flexion across the study period for each of the intervention groups. Over the initial three week period (control), the IFT (10.25 ± 2.44 SEM) and combination group (2.25 ± 2.67 SEM) appeared to improve in degrees of knee flexion. However in the same period, the exercise therapy group appeared to decrease flexion range of motion (1.42 ± 5.04 SEM).

Over the intervention period both the exercise therapy group (10.25 ± 3.52 SEM) and the combination group (4.48 ± 3.66 SEM) appeared to increase flexion range of motion.

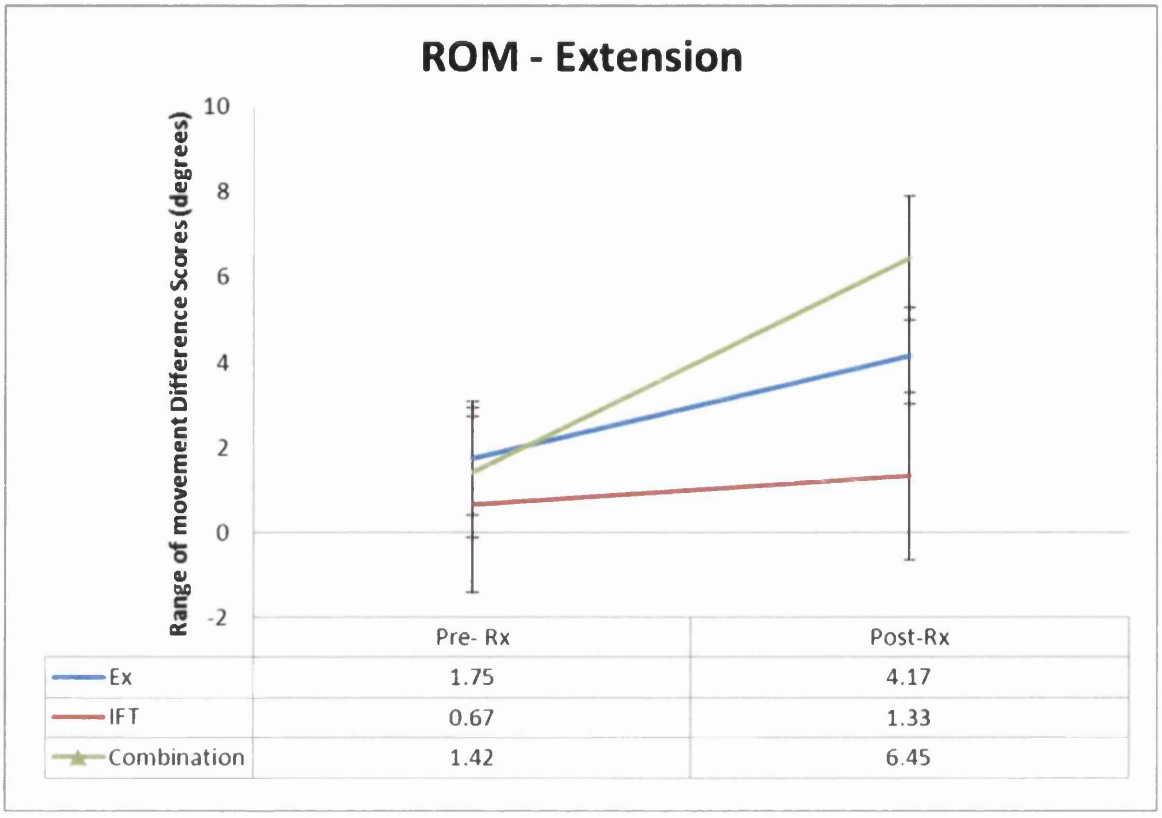
However, over the same period the IFT decreased in flexion range of motion (3.42 ± 3.52 SEM).

Over the study period all groups demonstrated an improvement in flexion range of motion. Statistically, normality tests proved the data collected for flexion range of motion to be parametric, thus ANOVA tests were used to analyse the data. For between group differences, Bonferroni post-hoc tests were used.

Between group analysis demonstrated that there was a significant difference ($p=0.015$) found between the exercise therapy and IFT groups over the intervention period. No other significant between group differences were found.

A one-way repeated ANOVA was conducted to compare flexion ROM before the control period, prior to treatment and following treatment. Significant improvements in flexion ROM, in the exercise therapy group were found in both the intervention period ($p=0.015$) and in the overall study period ($p=0.05$).

Extension



	Pre- Rx	Post-Rx
Ex	1.75	4.17
IFT	0.67	1.33
Combination	1.42	6.45

Graph 4. Changes in knee extension during the intervention period across all groups.

The graph above shows changes in knee extension range of motion in subjects over the study period. All groups appear to have demonstrated improvements over all periods during the study.

Statistically, normality tests proved the data collected for extension range of motion to be significantly different from normal distribution therefore Kruskal-Willis and Wilcoxon tests were used for between group and within group analysis respectively. Following statistical testing, no significant between group differences were found.

Within group analysis using Wilcoxon tests demonstrated a significant improvement ($p=0.009$) in the exercise therapy group over the study period. A significant improvement

(p=0.007) was also demonstrated over the same period in the combination group. The combination group also demonstrated a significant improvement (p=0.027) over the intervention period.

3.9 Summary

Overall, there appeared to be a general improvement across all outcomes in all groups (see Table 10 below), other than in ROM flexion in the IFT group. However, significant improvements were demonstrated for all outcomes in the exercise therapy group. The IFT group did not demonstrate any significant improvement in any of the outcomes measured. Furthermore, it does appear that the addition of IFT to exercise therapy does have relevance as the combination group appeared to be of most benefit to subjects in the study when assessing extension ROM.

Table 10: Summary Table of Results

	Outcome	Pre Treatment score	Post Treatment score	Improvement	*P* value
Combination Group	WOMAC	-0.67	-41.91	Improvement of 41.24	*P*=0.026
	Pain	-0.17	-2.36	Improvement of 2.19	*P*>0.05
	ROM Flexion	2.25	6.73	Improvement of 4.48	*P*=0.05
	ROM Extension	1.42	6.45	Improvement of 5.03	*P*=0.027
IFT Group	WOMAC	-7.83	-25.67	Improvement of 17.84	*P*>0.05
	Pain	0.58	-0.25	Improvement of 0.83	*P*>0.05
	ROM Flexion	10.25	6.83	Worsened by 3.42	*P*>0.05
	ROM Extension	0.67	1.33	Improvement of 0.66	*P*>0.05
Exercise Therapy Group	WOMAC	7.83	-32.5	Improvement of 40.33	*P*=0.01
	Pain	0.33	-1.08	Improvement of 1.41	*P*=0.021

	ROM Flexion	-1.42	8.83	Improvement of 10.25	*P*=0.015
	ROM Extension	1.75	4.17	Improvement of 2.42	*P*=0.009

3.10 Discussion

In the current trial the effect of different interventions on subjects with OA of the knee has been examined. Originally, the aim of the study was to evaluate whether the combination of exercise therapy and IFT would have a greater benefit to sufferers of OA knee than either intervention alone. Following completion of the trial, it appears that for function (when measured by WOMAC), pain and flexion ROM, that the addition of IFT to an exercise therapy programme increased the benefit when compared to treatment using an exercise therapy programme in isolation.

Previously, combination treatments involving IFT on knee OA had not been tested on this type of population . This may be in keeping with the relatively little amount research done on IFT as a modality (Johnson 1999), or due to the increased complexity of examining numerous interventions in a single study. There is one other study known to the authors that has examined the effect of these combination treatments on an African population (Adedoyin 2005), and therefore the current trial planned to add knowledge to an area of relatively scant information, and test the methodology to plan a larger a scale study. Outcomes used to evaluate effectiveness of the interventions were the WOMAC scale, verbal pain scale and range of motion (ROM) measured with standard AMS goniometer. These outcomes were chosen as they have been proven to be reliable measures (Carlsson A 1983; Clapper 1988; Angst F 2001; Cibere 2004; Faucher M 2004), are regularly used within clinical practice, and have been commonly used in studies assessing similar measures as the current study (Adedoyin 2005; Walker 2006).

It was found that exercise therapy in isolation had a significant effect on pain (Pre-treatment 0.33 ± 0.79 (mean ± SEM) vs post-treatment -1.08 ± 0.63), flexion ROM (-1.42 ± 5.04 vs 8.83 ± 4.07), extension ROM (1.75 ± 1.34 vs 4.17 ± 1.13) and function (7.83

± 4.36 vs -32.5 ± 12.1) at various points of the study. IFT was found to have no significant effects on any outcome in isolation, however when used in combination with exercise therapy, significant improvements were found on function (0.67 ± 8.85 SEM vs -41.91 ± 16.53 SEM) and extension ROM (1.42 ± 1.53 SEM vs 6.45 ± 1.45 SEM). Improvements were greatest in the combination group.

3.11 Conclusion

The pilot study carried out appears to show that both exercise therapy and the combination of IFT to exercise therapy improves the outcomes measured when compared to either intervention in isolation. IFT in isolation did not demonstrate any significant changes in any of the outcomes measured. The trial carried out also planned to test the methodological process as a plan for any larger scale future trial. As the trial was carried out successfully, the trial does offer a valuable method of assessing these interventions in the treatment of OA knee.

The following chapter will examine the review and trial chapters, with comparison to any previous studies in the area and offer any possible explanation for the observed changes in the clinical trial study and to determine possible implications for future clinical practice.

4.0 Thesis Discussion

4.1 Introduction

Knee OA is a common disorder that affects millions of people worldwide (Naredo 2005). The disease is linked to an increase in age and with the age of the population set to increase, the prevalence of this condition is also likely to increase (Hamerman 1995). Furthermore the social cost of the condition is likely to increase and therefore it is important that a variety of methods are investigated so that society is able to adequately tackle the problems that this condition will present.

4.1.1 Aims and Objectives

The aim of the current thesis was to examine the current literature on the use of IFT and exercise therapy in the treatment of knee OA. Current trends were used to guide the design of a clinical trial which attempted to test the methodological design to guide a larger scale study which could answer whether the combination of IFT and exercise therapy would lead to greater improvements than either intervention alone.

4.2 Main Findings

This thesis has examined the existing literature on some of the possible methods that could be used to address some of the common symptoms that knee OA is likely to present. The review chapter presented some of the possible mechanisms of IFT and highlighted that it may be a viable option to decrease pain caused by inflammatory disorders such as knee OA and to aid in function. The review also highlighted the need for more structured research in the area, and into the exact mechanisms that caused IFT to have its effects.

The review chapter also described the use of exercise therapy on knee OA and presented encouraging signs that this method is a useful and easily applicable method with which to address many of the common symptoms of knee OA. The majority of studies encouraged the further use of exercise therapy and also highlighted potential problems in this body of research. The review highlighted difficulties in comparisons of studies due to the wide varieties of exercise methods, repetitions; frequencies used and suggested the need for some parity when designing studies to assess the modality.
As part of the thesis a pilot study was designed to assess whether the combination of the two aforementioned treatments would have significant effects when compared to either treatment modality in isolation, and to test the viability of a similar larger scale study. Although the pilot-study did demonstrate a small benefit of combination therapy, the effect was minimally more beneficial than exercise therapy in isolation and therefore it could be questioned as to the cost effectiveness of the addition of IFT to an exercise programme for knee OA.

4.2.1 Hypoalgesia of IFT

When compared to other studies that have examined the effect of IFT on pain, the current study was unable to demonstrate any significant improvement in pain, although a clinical improvement in pain was observed, thus in agreement with other studies (Adedoyin 2002; Hurley 2004). As in other studies (Hurley 2004) a clinical improvement is one that is insignificant post analysis, but keeps with a positive trend and is one that may be viewed by the subject to be worthwhile, i.e. from a mean rating of 0.58 at the end of the control period to -0.25 post intervention as illustrated in Graph 2. In contrast to the current study however, improvement with regards to pain in other studies was proved to be significant (Johnson 1999; Jarit 2003; Johnson 2003; Adedoyin 2005; Jorge 2006; Mcmanus 2006).
In the present study, IFT was used for 20 minutes with a sweep setting between 80Hz and 120Hz beat frequency. These settings are in keeping with previous authors' work, as outlined in the narrative review chapter of the current study. Most other studies used 100Hz at a constant beat frequency (Johnson 1999; Johnson 2003; Mcmanus 2006; Walker 2006), therefore it may be that 100Hz is the optimum frequency for pain relief, as most studies

reviewed that used this frequency appeared to find significant improvements on pain relief. Other authors propose that frequencies of 100Hz or above selectively stimulate large diameter nerve fibres, inducing segmental inhibition of nociceptive nerve impulses in the substantia gelatinosa of the dorsal horn (De Domenico 1981; Savage 1992; Walsh 1997). It is interesting to note that a significant effect on pain was found in a similar study (Adedoyin 2005) using 80Hz frequency as this is contradictory to the supposed mechanism of action in terms of inhibition of large diameter fibres, which supposedly occurs above 100Hz. However, it has been postulated that frequencies above 40Hz may cause a physiological pain block (De Domenico 1982; Brown 1985; Goats 1990). The Adedoyin (2005) study used IFT as often as the current study, and also applied the intervention using a quadrapolar method. The main differences being the beat frequency used and every subject in the intervention group in the Adedoyin (2005) study received exercise therapy treatment. There are a number of other treatment variables that need to be considered when analysing the effects demonstrated in the present study. Frequency of application, duration of treatment, electrode placement and length of intervention period may all affect the ability of IFT to have a significant effect on pain. In the current study, IFT was applied twice a week, whereas in other studies IFT has been applied two or three times a day (Jarit 2003; Walker 2006) . This frequency of treatment may be considered unrealistic in any setting other than in a home setting due to resources of staff and equipment, thus would be therefore clinically inapplicable. The present study used a treatment duration of 20 minutes as this is considered as the average treatment duration in clinical practice, however in some of the studies reviewed, IFT was applied for up to one hour (Jorge 2006). This may be considered as unrealistic in the clinical environment as the average physiotherapy treatment lasts about 30 minutes.

Some of the studies reviewed treated subjects for up to sixteen weeks (Walker 2006) whereas the current study had no follow up period, with the intervention period lasting three weeks. This was mainly down to resources available to the current authors, and is an aspect that any future study would look to address.

4.2.2 IFT Effect on Function

IFT studies that examined the effect on function found similar findings to that of the present study. Hurley et al. (2004) found a clinical improvement in function, although this was not proved to be significant. In contrast, Adedoyin et al. (2005) found a significant improvement in WOMAC score following use of IFT at 80Hz beat frequency for 20 minutes, twice a week for four weeks. However, the fact that every intervention group in this study received exercise therapy meant that the IFT group in the Adedoyin (2005) study was in effect, a combination treatment group. In the study, functional improvement was attributed to the effect of IFT, however it could be argued that the improvement in function could be attributable to the effect of the exercises used in the study.

However, Hurley (2004) found that the addition of manipulative therapy to an IFT programme yielded significantly better results than the manual therapy group, thus in contradiction to the present study. Hurley (2004) used IFT at a constant frequency of 140Hz, for 30 minutes per treatment session but only gave an average of five treatment sessions. Thus, it may be that constant frequencies yield better results when using IFT for functional improvement.

4.2.3 IFT Effect on Range of motion

The remaining outcome measure used in the current study was ROM using goniometer. None of the studies examining IFT used ROM as an outcome measure, thus comparison in respect of this outcome is made difficult. The measurement of ROM is much more common when analysing the effect of exercise therapy on knee OA.

4.2.4 Exercise Therapy on Hypoalgesia

In the present study, the exercise therapy group was the only intervention group that demonstrated a statistical improvement in pain over the intervention period. Although the other groups appeared to demonstrate an improvement, only the exercise therapy group

showed a significant change. This finding was in agreement with other studies mentioned previously in chapter 2 (Ettinger 1997; Rogind 1998; O'Reilly 1999; Deyle 2000; Thomas 2002; Huang 2003; McCarthy 2004; Deyle GD 2005; Huang 2005; Doi 2008; Jan 2008). However although there seems to be a favourable effect of exercise therapy, the types of exercise used in the various studies ranges from high resistance, low repetition exercise to aerobic, class based exercise. The muscle groups that are targeted with the exercises used also varies from quadriceps to lumbar region. Therefore, due to the wide variety of exercise used, clear comparison is difficult. The present study used easily applicable exercises that are commonly used in practise in a circuit method at an intensity that was comfortable for the subjects in the study. Subjects were encouraged to continue with the exercises at home if they wished. This was also aimed to replicate clinical practise as patients often have to continue with exercises at home as part of a treatment plan.

The present study found a significant reduction in pain, however, a number of other studies found no significant difference in osteoarthritic knee pain when treating subjects with exercise. Williamson et al (2007) demonstrated an improvement in pain scores which was not significant. The exercises used in this study were similar to the ones used in the present study, as they used clinically applicable exercises that concentrated on quadriceps and hamstring exercises such as straight leg raise, balance exercises, sit-to-stand, stair climbing and resisted knee extension. This exercise group exercised under supervision for one hour per week over six weeks but did not exercise at home. It may be considered that if this group were allowed to exercise at home, then a significant reduction similar to the present study may have been achieved.

Bennell et al. (2005) compared 'physiotherapy' management which included exercise against a placebo in the treatment of knee OA. The exercises used were devised to retrain the quadriceps, hip, back and thoracic spine. Compliance with the exercises was monitored with log book however as the exercise detail in the study is relatively scant and due to the exercises being combined with a number of different interventions, it is difficult to compare the current study accurately. The Bennell study reported that 53% of the physiotherapy

group reported a significant reduction in pain, compared with 47% in the placebo group, thus there being no significant between group differences.

4.2.5 Exercise Therapy effect on function

Function in the present study was measured using the WOMAC scale which is a scale used in a number of the studies compared earlier in chapter 2. (Maurer 1999; O'Reilly 1999; Deyle 2000; Thomas 2002; McCarthy 2004; Bennell 2005; Deyle GD 2005; Doi 2008; Jan 2008). The present study found that both the exercise therapy group and the combination group found a significant improvement in WOMAC score during the intervention period. This significant improvement in WOMAC score is in keeping with the findings of a number of other studies (O'Reilly 1999; Deyle 2000; Thomas 2002; Deyle GD 2005; Jan 2008) regardless of exercise type used. This suggests that general exercise, regardless of fine detail can lead to a significant improvement in activities of daily living and overall function.

4.2.6 Exercise Therapy effect on range of movement

In the present study, subjects in the exercise therapy group improved in flexion and extension range of motion significantly. Between group analysis also demonstrated a significant difference in the exercise therapy group over the IFT group. The only other similar study (Huang 2005) to examine the effect of exercise therapy on ROM found that flexion and extension ROM increased significantly in all treated groups. Exercises used in this study involved the used of a Kin-Kom machine which helps strengthen the knee at different degrees of knee flexion. Although the exercise programme used in this study differs to that used in the present study, it could be that the prolonged positioning of the affected knee in differing degrees of flexion led to stretching of the knee joint capsule. This may have occurred in the present study as a number of the exercises used could feasibly have had this affect (hamstring curl, passive knee flexion, cycling).

4.2.7 Effect of Combination Treatment on outcome measures

The only studies known to the authors that have used the same combination treatments are those carried out by Adedoyin et al. (2002) and (2005). In the former study, IFT was used as the treatment and this was compared to a 'placebo' group, although all participants, including those in the placebo group received eight, 20 minute exercise sessions over four weeks. The IFT in the study was set at 100Hz for the first fifteen minutes and then reduced to 80Hz for the final five minutes and participants in the IFT group underwent this treatment following the exercise. The study found that both groups found a significant reduction in pain, and furthermore there was a significant difference between groups. This result suggests that both the IFT and exercise therapy is effective at reducing pain, although details of the exercises that subjects undertook are not documented in the study.

In the 2005 study, the author assessed the effect of IFT, TENS, and exercise on knee OA. However, in the study all groups received exercises which consisted of eight sessions of quadriceps strengthening exercises and cycling for a total of approximately 25 minutes. The IFT used in the study consisted of a continuous beat frequency at 80Hz at a strong but comfortable intensity. In the 2005 study, WOMAC was added to pain rating as an outcome measure and the study found that all groups had a significant improvement in pain and WOMAC score over the four week period which is in agreement with the present study. However, the present study was not able to demonstrate a significant reduction in pain in the combination group, although this was adjudged to be clinically significant.

4.2.8 Outcome Measures

The current study used WOMAC as the main outcome measure. This outcome has been proven to be reliable (Angst F 2001; Faucher M 2004) and is commonly used in arthrogenic studies to detect any change in function. However, it may be argued that although it is a commonly used measure in clinical trials, it is not commonly used in clinical practice, and

it is suspected that this may be due to the overall cost of the scale. It could also be argued that another less common functional scale such as 'timed get up and go' or 100m walk test could have been used. It was therefore decided that due to limited time resources, and in keeping with studies within the area that the main functional outcome would be the WOMAC scale.

A verbal pain rating scale was used in the study to evaluate pain as this is a scale commonly used in clinical practice. Subjects were asked to rate their pain at worst between 0-10 over the past 24 hours. Although it has been proved that this is a valid and reliable measure to use (Geier 2007), one could argue that the outcome may not be as sensitive as a rating between 0-100, which may allow for a more accurate detection of any change in pain rating. It may also be argued that other pain specific questionnaires such as the Mcgill pain questionnaire (Melzack and Torgerson, 1971) could have been used in place of, or in addition to the NRS. This was considered, however in keeping with clinical practice and due to limited resources, the NRS was the only pain measure used.

The final outcome used was ROM of the knee as measured by goniometer. This measure is a commonly used measure in physiotherapy and the reliability has been confirmed by other authors in previous studies (Rothstein 1983; Clapper 1988; Cibere 2004). The measurement is used within clinical practice to give the examiner an idea of the flexibility of the joint, and thus the overall health of the joint being tested. Reliability measures of data showed that measurements for flexion and extension fell within 95% confidence limits, thus were of high reliability.

Overall the outcomes used are all outcomes that are easily able to be used in clinical practice in any outpatient department. It could be argued that the outcomes may not be as sensitive as other more expensive outcome measures (Kin-kom to measure muscle strength or electro-goniometry) and it could also be argued that the study could have used more outcomes to measure function, such as the SF-36 scale, or timed 10metre walk test. However, based on the time available the study ensured that the most common clinical measures were assessed using reliable formats. Although the study did aim to try and

replicate similar treatments and outcomes used in the clinical setting, it is recognised that there were limitations to the study.

4.3 Limitations

Overall, the present study has found similar results to previous studies when examining the effects of exercise therapy and IFT on knee OA. However, the present study is one of two known to the authors that has trialled combination therapy on the chosen condition. There are many studies that have examined each intervention in isolation, however the examination of combination therapies is less common and the possible reasons for this have been discussed earlier. The design of the present study is also less common. In the present study, each subject acted as their own control over the initial three week period. This meant that the authors were able to include a control group without the clinical loss to the patient of not receiving any treatment. It could be argued that due to subjects acting as their own control, the disadvantage of intervention subjects being compared to control subjects with other potentially confounding variables is not a concern. It may also be argued that as all subjects knew that they were to receive treatment in the second three week period of the study, that a 'cognitive-dissonance effect' may have caused the subjects to behave in a manner that would not have been keeping with their normal behaviour had they not been due to receive treatment. With a linear control group throughout a study, it is possible to evaluate the effect of no intervention across the whole study period, and due to restrictions following ethical review, this was not possible during the current study.

The present study evaluated the interventions over a six week period and there was no follow up done on subjects on completion of the intervention period. This denies the authors potentially valuable information on the longer term effect of the intervention. Had resources been available to the authors, subjects would have been evaluated over a six month period following completion of the intervention phase.

The study was a pilot study; therefore any findings must be viewed with caution as they may not be applicable to the general population. Due to time and staffing resources, it was decided that this would be the most realistic option when compared to the option of starting with a multi-centre trial. No power calculation was done prior to subject allocation, and subject number was based on similar studies that had examined similar interventions (Adedoyin 2002, 2005). There was no follow up period on subjects following completion of the trial. This means that any longer term effects of interventions were not assessed and this makes true evaluation of cost-effectiveness of each intervention difficult. Although the combination intervention group showed most improvement, it could be questioned as to whether the degree of improvement is cost effective when the extra treatment time of the therapist is also considered, and this could be a question of future research. However, even though it is recognised that there were limitations to the study, it is possible that the study can shape future research into the area, as the study does demonstrate that combination treatments on OA knee can have beneficial effects.

4.4 Conclusion

The results of the study show that the interventions tested can have a positive effect on people living with knee OA. This is largely in agreement with other studies done in the area, as reviewed in chapter 2. It was also demonstrated that the largest effect took place in the combination group for the improvement of extension ROM. The effect of combination therapy needs to be studied in more detail, possibly using a multi-centre trial and group exercise classes. This would improve cost-effectiveness and hopefully maintain effect of intervention. It appears from past research that the most effective frequency for IFT use is 100Hz, and therefore, it may be that any future study uses this frequency when assessing the effect of IFT on knee OA. The exercises used in the current study are simple to apply and are commonly used in clinical practice, thus it would be appropriate to continue their use in any future study.

The effect of exercise therapy on knee OA has previously been examined by a number of studies, and therefore the current study adds little to the work on this area However, the use of IFT on OA knee is relatively scant therefore the study adds to the work done on examining the effect of IFT on knee OA.As far as the author is aware, this is the first study that has looked at the effect of each of these modalities in isolation and in combination in this population, and as a result contributes originally to the body of knowledge on the area. The results from the clinical suggest that exercise therapy should be the mainstay of future treatment, with combination treatment used if available. The study also suggests further ways in which future research may be structured in order to make comparison more viable and thus more valuable. The thesis has addressed its initial aims through evaluation of the current research and the presentation of a repeatable pilot study.

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Appendix 1

Appendix 1

Search	Keywords	Database	No. of Hits	No. of Papers Identified
1	Osteoarthritis	PUBMED	23554	
2	OA		5924	
3	Arthritis		100475	
4	Exercise		109604	
5	Exercise Therapy		10742	
6	Rehabilitation		151403	
7	Active Rehabilitation		4409	
8	Physical Therapy		47197	
9	Physiotherapy		46695	
10	Physical Activity		46000	
18	Knee OA		2016	
19	#1 + #4		765	
20	#1 + #5		385	
21	#1 + #6		1695	
22	#1 + #7		83	4
23	#1 + #8		806	
24	#1 + #9		765	
25	#1 + #10		526	
26	#2 + #4		248	
27	#2 + #5		117	
28	#2 + #6		378	
29	#2 + #7		18	5
30	#2 + #8		190	
31	#2 + #9		184	
32	#2 + #10		169	
33	#3 + #4		1548	
34	#3 + #5		683	
35	#3 + #6		3996	
36	#3 + #7		226	
37	#3 + #8		1703	
38	#3 + #9		1649	
39	#3 + #10		839	
40	#18 + #4		166	
41	#18 + #5		88	35
42	#18 + #6		239	
43	#18 + #7		13	
44	#18 + #8		134	
45	#18 + #9		131	
46	#18 + #10		134	
273	#1	Web Of Knowledge	21827	
274	#2		10889	
275	#3		100000	
276	#4		100000	
277	#5		11125	
278	#6		57554	
279	#7		1846	
280	#8		19748	
281	#9		4802	
282	#10		53256	
290	#18		2775	
291	#1 + #4		899	
292	#1 + #5		291	

293	#1 + #6		528	
294	#1 + #7		42	2
295	#1 + #8		432	
296	#1 + #9		129	
297	#1 + #10		556	
298	#2 + #4		271	
299	#2 + #5		95	23
300	#2 + #6		104	
301	#2 + #7		6	1
302	#2 + #8		144	
303	#2 + #9		24	1
304	#2 + #10		178	
305	#3 + #4		1227	
306	#3 + #5		368	
307	#3 + #6		776	
308	#3 + #7		64	
309	#3 + #8		813	
310	#3 + #9		226	
311	#3 + #10		1128	
312	#18 + #4		209	
313	#18 + #5		90	5
314	#18 + #6		86	7
315	#18 + #7		6	
316	#18 + #8		132	
317	#18 + #9		22	
318	#18 + #10		147	
515	Osteoarthritis	CINAHL/ MEDLINE	26603	
516	OA		13328	1
517	Arthritis		86290	
518	Exercise		153777	
519	Exercise Therapy		10887	
520	Rehabilitation		179665	
521	Active Rehabilitation		165	
522	Physical Therapy		34873	
523	Physiotherapy		10382	
524	Physical Activity		31332	
532	Knee OA		1051	
533	#1 + #4		1368	
534	#1 + #5		387	
535	#1 + #6		1700	
536	#1 + #7		2	
537	#1 + #8		655	
538	#1 + #9		218	
539	#1 + #10		353	
540	#2 + #4		475	
541	#2 + #5		132	
542	#2 + #6		486	
543	#2 + #7		1	
544	#2 + #8		160	
545	#2 + #9		75	10
546	#2 + #10		138	
547	#3 + #4		1622	
548	#3 + #5		400	
549	#3 + #6		2573	
550	#3 + #7		1	
551	#3 + #8		859	

552	#3 + #9		217	
553	#3 + #10		448	
554	#18 + #4		174	
555	#18 + #5		64	22
556	#18 + #6		144	
557	#18 + #7		0	
558	#18 + #8		63	8
559	#18 + #9		27	
560	#18 + #10		58	

Appendix 2

Patient Information Sheet

Study Title

Comparing the effect of two different types of physiotherapy treatment on knee pain.

Your Invitation to the Study

You are invited to take part in a research study, but before you do, it is important you read the information below to understand what the research involves so you can decide if you wish to be involved. Please take some time to read the information and feel free to contact one of the investigators to ask any questions you may have.

Purpose of the Study

The purpose of the study is to see whether the combination of two commonly used physiotherapy treatments work better than one alone. The reason for the study is to see if there is any particular treatment that is best for knee pain.

Why have I been asked to take part?

You have been chosen to take part in this study as you have been diagnosed with a certain type of knee pain (arthritis) by your doctor.

Do I have to take part?

No, you do not have to take part. If you choose to take part in the study it is at your own free will. Also, if you do choose to take part, you do have the right to pull out of the study at any time, without giving a reason.

What will happen if I take part?

If you decide to take part you will need to contact the investigator using the contact details given below.
When you make contact, you will be asked for your contact details and be given an appointment to see a physiotherapist at Singleton Hospital.
During the first appointment at Singleton hospital you will be given the chance to ask any questions and asked to sign a consent form. When you sign the consent form, it means you are giving consent for the researchers to randomly allocate (put you into a group at random) you to receive one of three different types of treatment. You are also giving consent for us to contact your GP to make them aware of your taking part in the study, and for the researchers to collect some personal information for the purpose of the study. After signing the form you will have a simple assessment by a physiotherapist that will last about 20 minutes.
You will then be given another appointment for 3 weeks after that initial assessment. At this appointment you will have the same assessment to check for any changes, but then you will start your treatment.

You could have any of the following types of treatment:

1. A pain relieving treatment called Interferential Therapy
2. Exercises
3. A combination of the above treatments.

The type of treatment that you receive will be decided randomly so you will not have the ability to decide on which treatment you have. The type of treatment is decided randomly to try and keep the study fair and free from any effect that could alter the results.
Depending on what treatment you have, the time you are treated for could be between 25 and 50 minutes. You will need to attend Singleton Hospital for treatment twice a week for three weeks.
Following the three week treatment period you will be assessed again. This will complete your involvement in the study. At the end of this period, if you are not happy with the treatment you have received or wish to have more physiotherapy treatment, you can be placed on the physiotherapy waiting list.

What do I have to do?

All you need to do is read this sheet and if you wish to take part in the study, then contact an investigator whose contact details are given below.

What are the possible disadvantages and risks of taking part?

There are no common or expected risks by taking part.

What are the possible benefits of taking part?

It is hoped that by taking part in this study you could have less pain in your knee, have more strength in the muscles around your knee, have more movement at your knee and improve your ability to carry out daily tasks.

Will my taking part in this study be kept confidential?

Yes. As soon as you provide details, these will be given a number. The only people who will see these details are the people carrying out the study and they have to keep them safe.

Who will have access to the information I have provided?

Only the people carrying out the study will have access to the information you have provided.

What will happen to the results of this study?

The results will be stored at Swansea University for 10 years, as instructed by law. You will be able to see the results of the study if you wish to do so.

Will I receive travel costs?

Yes, travel costs will be paid. You will receive 23p per mile, up to a total of 10 miles per return journey (5 miles each way) to Singleton Hospital. Any travel costs will be paid at the end of your involvement within the study. To claim the travel costs you will need to fill in an expense form which one of the researchers will be happy to help you with.

Who has funded the study?

Sponsorship and funding of this study has been supplied by University of Wales, Swansea.

Who has reviewed this study?

This study has been reviewed by the student research committee and supervisors within the School of Health Science at the University of Wales, Swansea. It has also been presented to fellow researchers and physiotherapists for feedback.
This study has been reviewed by The South-West Wales Research Ethics Committee.

Contact for further information

Thank you for taking time to read about this study. To take part or for any further questions please contact:

Craig Dyson
E-Mail: 491747@swansea.ac.uk
Tel: 01792 543564

Gareth Noble (Supervisor)
E-Mail: j.g.noble@swansea.ac.uk
Tel: (01792) 602026

Appendix 3

Consent Form

Title of Project: Assessing the Effect of Interferential Therapy and Exercise therapy on OA Knee.

Name(s) of Researcher(s): Craig Dyson, Gareth Noble, Ron van Heeswijk

Please initial box

1. I confirm that I have read and understand the information sheet dated..... for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by the individuals outlined above, where it is relevant to my taking part in the research. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the above study. ☐

Name of Patient	Signature	Date
Name of person Taking consent	Signature	Date

Appendix 4

All studies except clinical trials of investigational medicinal products

REC Ref:	08/WMW02/76
Short Title of Study:	Assessing the effect of Exercise Therapy and IFT on OA Knee
CI Name:	Mr Jonathan C Dyson
Sponsor:	Swansea University

Please complete this checklist and send it with your application

- Send ONE copy of each document (except where stated)
- ALL accompanying documents must bear version numbers and dates (except where stated)
- When collating please do NOT staple documents as they will need to be photocopied.

Document	Enclosed?	Date	Version	Office use
Covering letter on headed paper	○ Yes ○ No			
NHS REC Application Form, Parts A&B	Mandatory			
Site–Specific Information Form (for SSA)	○ Yes ○ No			
Research protocol or project proposal (6 copies)	Mandatory			
Summary C.V. for Chief Investigator (CI)	Mandatory			
Summary C.V. for supervisor (student research)	○ Yes ○ No			
Research participant information sheet (PIS)	○ Yes ○ No			
Research participant consent form	○ Yes ○ No			
Letters of invitation to participants	○ Yes ○ No			
GP/Consultant information sheets or letters	○ Yes ○ No			
Statement of indemnity arrangements	○ Yes ○ No			
Letter from sponsor	○ Yes ○ No			
Letter from statistician	○ Yes ○ No			
Letter from funder	○ Yes ○ No			
Referees' or other scientific critique report	○ Yes ○ No			
Summary, synopsis or diagram (flowchart) of protocol in non–technical language	○ Yes ○ No			
Interview schedules or topic guides for participants	○ Yes ○ No			
Validated questionnaire	○ Yes ○ No			
Non–validated questionnaire	○ Yes ○ No			
Copies of advertisement material for research participants, e.g. posters, newspaper adverts, website. For video or audio cassettes, please also provide the printed script.	○ Yes ○ No			

An application form specific to your project will be created from the answers you give to the following questions.

1. Is your project an audit or service evaluation?

○ Yes ◉ No

2. Select one research category from the list below:

○ Clinical trials of investigational medicinal products
○ Clinical investigations or other studies of medical devices
◉ Other clinical trial or clinical investigation
○ Research administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
○ Research involving qualitative methods only
○ Research limited to working with human tissue samples and/or data
○ Research tissue bank

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

○ Other research

2a . Please answer the following questions:

a) Does the study involve the use of any ionising radiation?	○ Yes	◉ No
b) Will you be taking new human tissue samples?	○ Yes	◉ No
c) Will you be using existing human tissue samples?	○ Yes	◉ No

3. Is your research confined to one site?

◉ Yes ○ No

4. Does your research involve work with prisoners?

○ Yes ◉ No

5. Do you plan to include in this research adults unable to consent for themselves through physical or mental incapacity?

○ Yes ◉ No

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

◉ Yes ○ No

6a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

○ Yes ◉ No

NHS Research Ethics Committee NHS Application form

This form should be completed by the Chief Investigator, after reading the guidance notes. See glossary for clarification of different terms in the application form.

Short title and version number: (maximum 70 characters – this will be inserted as header on all forms)
Assessing the effect of Exercise Therapy and IFT on OA Knee

Name of NHS Research Ethics Committee to which application for ethical review is being made:

Project reference number from above REC: 08/WMW02/76
Submission date: 21/08/2008

A1. Title of the research

Full title: Assessing the effect of Exercise Therapy and Interferential Therapy on OA Knee: A feasability study.

Key words:
Osteoarthritis
OA
Arthritis
Exercise
Exercise Therapy
Rehabilitation
Active Rehabilitation
Physical Therapy
Physiotherapy
Physical Activity
Electrotherapy
Electrical Stimulation
TENS
IFT
US
Ultrasound
PSWD
Knee OA

A2. Chief Investigator

Title:	Mr
Forename/Initials:	Jonathan C
Surname:	Dyson
Post:	Physiotherapist
Qualifications:	BSc(Hons) Physiotherapy
Organisation:	Vale Clinic
Work Address:	Vale Clinic Hensol
Post Code:	CF72 8JY
E-mail:	jc_dyson@hotmail.co.uk
Telephone:	01792204546

Fax:

Mobile: 07789394082

A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application

A3. Proposed study dates and duration

Start date: 01/10/2008
End date: 01/09/2009
Duration: Years: 1 ; Months: 0

A4. Primary purpose of the research: *(Tick as appropriate)*

- ☐ Commercial product development and/or licensing
- ☐ Publicly funded trial or scientific investigation
- ☑ Educational qualification
- ☐ Establishing a database/data storage facility
- ☐ Other

Question(s) 5 disabled.

A6. Does this research require site-specific assessment (SSA)? (Advice can be found in the guidance notes on this topic.)

○ Yes ◉ No

If No, please justify:

Data Collection will take place in the Physiotherapy Department of Singleton Hospital (Abertawe Bro-Morgannwg University Trust). Data collection will only utilise equipment currently held in the department for its intended use. Investigation falls within routine clinical competence, as the methods being investigated are part of routine physiotherapy practice.

If Yes, an application for SSA should be made for each research site on the Site-Specific Information Form and submitted to the relevant local Research Ethics Committee. Do not apply for SSA at sites other than the lead site until the main application has been booked for review and validated by the main Research Ethics Committee.

Management approval to proceed with the research will be required from the R&D office for each NHS care organisation in which research procedures are undertaken. This applies whether or not the research is exempt from SSA. R&D applications in England, Wales and Scotland should be made using the Site-Specific Information Form.

A7. What is the principal research question/objective? *(Must be in language comprehensible to a lay person.)*

The primary objective of the proposed study is to evaluate the effectiveness of exercise therapy and interferential therapy in the management of OA knee as determined by pain, range of motion, physical function and Quality of Life measures. Baseline measurements using standardised objective tests would be taken pre and post treatments and effectiveness of treatments would then be evaluated.

A8. What are the secondary research questions/objectives? *(If applicable, must be in language comprehensible to a lay person.)*

Secondarily, it is to ascertain whether these treatment options would be more or less effective as a combination therapy.

A9. What is the scientific justification for the research? What is the background? Why is this an area of importance? *(Must be in language comprehensible to a lay person.)*

Osteo-Arthritis (OA) is one of the most prevalent disease associated with significant disability as well as a common cause of functional limitation and dependency (Devos-Comby et al. 2006) that affects the major joints of the musculoskeletal system (especially the hip and knee joints) and has a high prevalence in the older population due to the 'wear and tear' component in its pathogenesis. In the United States, OA was the leading cause of disability, with the indirect cost estimated to be $68.4 billion in 1992 (Yelin and Callaghan, 1995). It has been projected that 59.4 million in the U.S. (or 18.2% of the population) will suffer from OA by 2020 (MMWR, 1994). As a condition, OA of the knee is particularly disabling due to symptoms such as pain, stiffness and muscle weakness (Mcalindon et al. 1992, O'Reilly et al. 1998). As the population ages, the cost of this public health burden is expected to increase. Increased treatment efforts and appropriate clinical and self-management are needed to reduce the impact of arthritis and chronic joint symptoms (MMWR, 2002). One aspect of the care of people living with OA of the knee involves the referral to a physiotherapist for symptom management aiming to decrease pain levels, muscle stiffness and weakness to ultimately improve their ability to carry out day to day activities(physical function) and quality of life (QoL). The mainstay of physiotherapy treatment is exercise therapy targeting the muscles that surround the knee to improve function. Furthermore, it is thought that if there is appropriate pain management via another physiotherapy treatment (i.e. interferential therapy), the persons' physical function and QoL may further increase. However, the strength of research evidence to support the use of both exercise therapy and interferential therapy is limited. Therefore, this research project would be aimed at improving the evidence base behind currently used treatment techniques within the realm of physiotherapy. The primary objective of the proposed study is to evaluate the effectiveness of exercise therapy and interferential therapy in the management of OA knee as determined by pain, range of motion, physical function and QoL measures. Secondarily, it is to ascertain whether these treatment options would be more or less effective as a combination therapy. Subjects would be split into one of four treatment groups; 1. Exercise Therapy, 2. Interferential Therapy, 3. A combination of 1. and 2., and 4. Control Group. Baseline measurements using standardised objective tests would be taken pre and post treatments and effectiveness of treatments would then be evaluated. The results of this study would inform physiotherapy practice with the aim of improving the management of OA knee for all people living with OA knee.

A10-1. Give a full summary of the purpose, design and methodology of the planned research, including a brief explanation of the theoretical framework that informs it. It should be clear exactly what will happen to the research participant, how many times and in what order.

This section must be completed in language comprehensible to the lay person. It must also be self-standing as it will be replicated in any applications for site-specific assessment on the Site-Specific Information Form. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.

The purpose of the planned study is to see whether the combination of exercise therapy and interferential therapy is more beneficial than either intervention alone when treating patient with osteo-arthritis of the knee.

It is planned to take thirty-six subjects, aged 45-70 all suffering with Osteo-arthritis (OA) of the knee who will be recruited from specialist GP clinics and consultant clinics around Abertawe Bro-Morgannwg University

NHS Trust. Subjects will have been referred into these clinics by their GP.

Inclusion Criteria are as follows:
1. Age 45–70
2. Confirmed osteo–arthritis (OA) of the knee by way of radiological investigation (X–Ray).
3. Osteo–arthritis as defined by (Altman 1986), i.e. the patient experiences pain and any five of the following:
1. Over 50 years of age,
2. Less than 30 minutes of morning stiffness,
3. Crepitus (noisy, grating sound) on active motion,
4. Bony tenderness,
5. Bony enlargement,
6. No palpable warmth of synovium,
7. Erythrocyte sedimentation rate (ESR) less than 40 mm/hr,
8. Rheumatoid factor less than 1:40 titer (agglutination method),
9. Synovial fluid signs.

Patients will be excluded from the study if they:

1. Have had any other treatment in the previous six weeks
2. Have any other medical condition which could explain their current complaints.
3. Have Kellgren Grade IV OA (large osteophytes (bony growths), marked joint space narrowing, severe sclerosis (hardening of the cartilage) and definite deformity of bone ends. This is applied when X–Ray shows a very high level of OA presence)(Kellgren 1957).
4. Are primarily suffering with patello–femoral joint OA (Osteo–arthritis of another joint)
5. Are contra–indicated for exercise treatment or Interferential Treatment (IFT). Contraindications for IFT are as follows: Patients whose skin are easily damaged or bruised, patients who are on anti–coagulation therapy, patients with pacemakers, patients who have active malignancy. Contraindications to exercise therapy are as follows: Any uncontrolled cardiac conditions(aortic stenosis,cardiac enlargement,dysrhythmias,ventricular aneurysm,cardiomyopathy,congestive heart failure) or uncontrolled metabolic disorders (Diabetes, thyrotoxicosis, myxedema.)
6. Are unable to read and understand English.

Procedure

Patients will be assessed for their suitability for the study in the GP/consultant clinic. If suitable, subjects will be given an information sheet about the study see attached). The information sheet will contain details of the investigation and state that they have the right to withdraw from the study at any time. The information sheet will also contain the contact details of the Chief Investigator. Subjects will be instructed to contact the Chief investigator if they wish to be included in the study. On contact with the Chief Investigator, patient name and contact details will be taken, and these details will be allocated to a number for randomisation. An appointment will be made to meet a physiotherapist who will act as the assessor of patient outcome. The physiotherapist will be blinded to the patient treatment. Informed consent will be obtained via a consent form issued prior to the start of the data collection process by the blinded physiotherapist. The blinded physiotherapist will carry out the following outcome measures during the initial assessment:

1. WOMAC Scale which consists of 24 questions, each corresponding to a visual analogue scale, designed to measure patients perceptions' of pain, stiffness and dysfunction.
2. Numerical Rating Scale (NRS) pain score. This is a numerical rating scale between 0–10. The patient is asked to rate their current pain on a scale of 0–10 with 0 meaning no pain and 10 meaning the worst pain imaginable.
3. Range of Movement. This will be a measurement of the patients knee flexion
and extension by the blinded physiotherapist.

This collection of data should take 20 minutes.

Following collection of the data, patients will be given another appointment three weeks following the initial assessment. This three week period will act as the control period. After three weeks, patients will again be assessed by the same blinded physiotherapist using the same outcome measures, and will commence the treatment procedure that they will have been randomly allocated.

Patients will be randomly allocated into one of three groups:

1. Interferential Therapy only group
2. Exercise Therapy only Group
3. Combined therapy group

IFT Group

Patients in the IFT group will receive IFT twice a week, for three weeks, i.e. six sessions in total. Each session will last for twenty-five minutes and IFT will be concentrated on the painful knee. Standardized IFT stimulation parameters for pain relief will be used: carrier frequency 3.85kHz; 80-120Hz sweep; pulse duration 130¼s. Four electrodes will be placed around the knee joint so as to concentrate the effect of the IFT into the centre of the joint and will be attached via a velcro strap to ensure maximum skin contact. IFT will be administered by the chief investigator.

Exercise Therapy Group

Patients in the exercise therapy group will also be treated twice a week for twenty minutes. The session will be broken up into the following format:
1. Warm up using static exercise bike x 3min at slow pace.
2. 6 exercise stations. Patient to exercise at each station for 40sec with 30 sec for change of station. Patient to complete circuit 3 times.
3. Warm down using static bike x 3min at slow pace
For example, each patient will do a warm up followed by the following circuit three times. After doing the circuit three times the patient will do the warm down.
Participants will carryout the following commonly used exercises:
1. Inner Range Quads in long sitting (sitting with legs on plinth and contracting thigh muscle).
2. Single Leg Balance. (Balancing on one leg)
3. Straight Leg Raise (sitting with legs on plinth and, keeping the leg straight, lifting the leg 2-3" off the bed).
4. Step Up Exercise (stepping up onto a step)
5. Passive Knee Flexion (the participant pulls their knee into a bent position)
6. Hamstring Curl (the participant lies on their front and bends their knee against gravity).
Patients in the Exercise group will be supervised by the chief investigator. Patients will be encouraged to continue with the exercises at home.

Combined Group

Patients in the IFT and Exercise group will do the above exercise regime and then receive 25 minutes of IFT set at the above parameters.

Control Group

Patients will act as their own control as they will be assessed following initial recruitment, wait three weeks to simulate a control period, then be assessed again prior to starting the treatment. For any patients complaining of increased symptoms following an exercise period, their exercise protocol would be modified accordingly on the opinion of the supervising physiotherapist.
Following completion of the study, patients will be offered conventional physiotherapy.
The second set of outcome measures will be recorded at least 48 hours after the last set of exercises to allow for any post-exercise stiffness.

Patients will be advised to continue using any medication prescribed prior to the start of the study, but will be excluded if any changes in analgesic medication occur during the study.
Patient name and contact details will be allocated to a reference number on allocation to the study. This data will be stored on password controlled university computers at Swansea University. This data will only be accessed by the Chief investigator and the research team. All assessment data recorded during the study will be kept in a sealed container in a lockable cabinet in Singleton Hospital. This will be accessed by the blinded physiotherapist carrying out the assessment, and the Chief investigator. Following completion of the study, all data will be stored at Swansea University for 10 years in compliance with the Data Protection Act 1998.

A10–2. In which parts of the research have patients, members of the public or service users been involved?

- ☐ As user–researchers
- ☐ As members of a research project group
- ☐ As advisor to a project
- ☐ As members of a departmental or other wider research strategy group
- ☑ None of the above

Please provide brief details if applicable:

A10–3. Could the research lead to the development of a new product/process or the generation of intellectual property?

○ Yes ◉ No ○ Not sure

A11. Will any intervention or procedure, which would normally be considered a part of routine care, be withheld from the research participants?

○ Yes ◉ No

A12. Give details of any clinical intervention(s) or procedure(s) to be received by research participants over and above those which would normally be considered a part of routine clinical care. *(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.)*

Additional Intervention	Average number per participant		Average time taken (mins/hours/days)	Details of additional intervention or procedure, who will undertake it, and what training they have received.
	Routine Care	Research		
Other	0	6	25mins	Intervention is exercise therapy to be delivered over 6 stations, each lasting for 40seconds per station. Participants will exercise at each station 3 times per session and do 2 sessions per week over 3 weeks.Therefore the total treatment time will be 150mins.
Other	0	6	25mins	Interferential Therapy (IFT) which will be delivered for 25minutes, twice a week over three weeks. Therefore total treatment time will be 150mins

A13. Give details of any non–clinical research–related intervention(s) or procedure(s). *(These include interviews, non–clinical observations and use of questionnaires.)*

Additional Intervention	Average number per participant	Average time taken (mins/hours/days)	Details of additional intervention or procedure, who will undertake it, and what training they have received.

A14. Will individual or group interviews/questionnaires discuss any topics or issues that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could take place during the study (e.g. during interviews/group discussions, or use of screening tests for drugs)?

○ Yes ◉ No

The Information Sheet should make it clear under what circumstances action may be taken

A15. What is the expected total duration of participation in the study for each participant?

The participants will be recruited from the primary sector (GP clinic)or from consultant led, hospital based clinics. Participants will then be given information on the study in the form of an information sheet. After voluntary participation in the study, baseline measurements using the Numerical Rating pain questionnaire, WOMAC function scale, and Range of Motion will be taken. These participants will wait for three weeks (to simulate waiting list times) and then be re-assessed using the same measures. After this, participants will be randomly allocated into one of three groups outlined earlier. This treatment will last for three weeks, with participants receiving treatment twice a week for up to one hour per session. Following the three week period, measurements using the outcome measures mentioned earlier will be repeated. At this stage the participants involvement in the study will end. They will then be offered further physiotherapy treatment if necessary.
Participants will undergo three sets of assessment lasting 15-20minutes per assessment. Participants in the exercise or IFT only group will receive treatments lasting for a total of 150minutes, split over 6 treatment sessions over a 3 week period. Participants in the combined treatment group(those receiving IFT and exercise therapy) will receive treatments lasting 300 minutes split over 6 treatment sessions over a 3 week period.

A16. What are the potential adverse effects, risks or hazards for research participants either from giving or withholding medications, devices, ionising radiation, or from other interventions (including non-clinical)?

All participants in this stduy will continue with routine treatment and medication.

A17. What is the potential for pain, discomfort, distress, inconvenience or changes to lifestyle for research participants?

There is no increased risk for any of these factors, other than those that may be experienced due to conventional physiotherapy treatment.

A18. What is the potential for benefit to research participants?

Potential benefit to research participants include decreased pain, increased range of motion at the knee joint, improved function and quality of life.

A19. What is the potential for adverse effects, risks or hazards, pain, discomfort, distress, or inconvenience to the researchers themselves? *(if any)*

None

A20. How will potential participants in the study be (i) identified, (ii) approached and (iii) recruited?
Give details for cases and controls separately if appropriate:

Potential participants for the study will be identified via specialist GP musculoskeletal clinics, and consultant-led hospital-based clinics. Patients will be informed of the study by the GP/consultant responsible for patient treatment. Patients will also be given an information sheet about the study with contact details of the chief investigator. If patients would like to be involved with the study they will contact the lead researcher/physiotherapy department that data collection will take place via telephone. An appointment will be made with a physiotherapist who will answer any questions and obtain written consent. This will complete the recruitment process.

A21. Where research participants will be recruited via advertisement, give specific details.

☑ Not Applicable

If applicable, enclose a copy of the advertisement/radio script/website/video for television (with a version number and date).

A22. What are the principal inclusion criteria? *(Please justify)*

1. Patients aged 45–70
2. Confirmed Knee Osteo–arthritis by way of Radiological investigation.

Patient age range chosen so as to include those most likely to suffer with OA knee. Confirmed Knee OA by way of radiological investigation to ensure diagnosis of condition being studied.

A23. What are the principal exclusion criteria? *(Please justify)*

1. Kellgren Grade IV Knee Osteo–arthritis of the knee
2. Patello–Femoral Joint Osteo–arthritis
3. Inability to read and understand English.
4. Patients suffering with pain from another source.
5. Exercise therapy or IFT in previous six weeks.
6. Any Contra–indications to Interferential Therapy/Exercise Therapy.

Patients with Kellgren grade IV osteo–arthritis have been excluded as physiotherapeutic intervention has been shown to be ineffective at this stage due to the advanced stage of degeneration of the affected joint.
Those patients with Patello–femoral OA have been excluded as this could reduce the validity and power of the study.
Those patients who are unable to read and understand English have been excluded as the patient information sheet and questionnaires issued (WOMAC) will be worded in English. Therefore if the patient is unable to understand this could decrease the validity of the study and reduce patient safety.
Patients with pain from another source and those who have received other treatment (exercise therapy or IFT) have been excluded as this could decrease validity of the study.
Those with any contra–indications to the treatments being studied have been excluded to ensure patient safety.

A24. Will the participants be from any of the following groups? *(Tick as appropriate)*

- ☐ Children under 16
- ☐ Adults with learning disabilities
- ☐ Adults who are unconscious or very severely ill
- ☐ Adults who have a terminal illness
- ☐ Adults in emergency situations
- ☐ Adults with mental illness (particularly if detained under Mental Health Legislation)
- ☐ Adults with dementia
- ☐ Prisoners
- ☐ Young Offenders
- ☐ Adults in Scotland who are unable to consent for themselves
- ☐ Healthy Volunteers
- ☐ Those who could be considered to have a particularly dependent relationship with the investigator, e.g. those in care homes, medical students
- ☐ Other vulnerable groups

Justify their inclusion.

☑ No participants from any of the above groups

A25. Will any research participants be recruited who are involved in existing research or have recently been involved in any research prior to recruitment?

○ Yes ◉ No ○ Not Known

If Yes, give details and justify their inclusion. If Not Known, what steps will you take to find out?

A26. Will informed consent be obtained from the research participants?

◉ Yes ○ No

If Yes, give details of who will take consent and how it will be done. Give details of any particular steps to provide information (in addition to a written information sheet) e.g. videos, interactive material.

If participants are to be recruited from any of the potentially vulnerable groups listed in A24, give details of extra steps taken to assure their protection. Describe any arrangements to be made for obtaining consent from a legal representative.

If consent is not to be obtained, please explain why not.

Patients will be issued with a consent form with the patient information sheet. The patients will be given the information sheet after being assessed for their suitability for the study by a consultant/GP/specialist physiotherapist. The patient will be required to sign and bring their consent form to the initial assessment.

Copies of the written information and all other explanatory material should accompany this application.

A27. Will a signed record of consent be obtained?

◉ Yes ○ No

If Yes, attach a copy of the information sheet to be used, with a version number and date.

A28. How long will the participant have to decide whether to take part in the research?

Patients will have the time from their being handed the information sheet in the clinic that they are initially assessed, up to the time they choose to be included and meet the physiotherapist for the first time. This period could be up to six months.

A29. What arrangements have been made for participants 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 etc.)*

Patients who do not understand English will be excluded from the study.

A30. What arrangements are in place to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

If any such information becomes available, patients will be informed and at all times and be offered the opportunity to exclude themselves from the study.

A30–1. 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 would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained. Any identifiable data or tissue would be anonymised or disposed of.
- ◉ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study.
- ○ 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:

Participants should be informed when seeking initial consent if it is planned to retain and make further use of identifiable data/tissue in the event of loss of capacity.

A31. Does this study have or require approval of the Patient Information Advisory Group (PIAG) or other bodies with a similar remit? *(see the guidance notes)*

○ Yes ◉ No

A32a. Will the research participants' General Practitioner (and/or any other health professional responsible for their care) be informed that they are taking part in the study?

○ Yes ◉ No

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

A32b. Will permission be sought from the research participants to inform their GP or other health professional before this is done?

○ Yes ◉ No

If No to either question, explain why not

If the participants GP refers to a specialist GP clinic or consultant clinic, responsibility of patients care passes to the specialist GP or consultant involved. Therefore, whoever refers the participant into the study will be the person responsible for the participants' care, thus the person responsible for participant care is informed.

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

A33. Will individual research participants receive any payments for taking part in this research?

○ Yes ◉ No

A34. Will individual research participants receive *reimbursement of expenses* or any other *incentives or benefits* for taking part in this research?

○ Yes ◉ No

A35. Insurance/indemnity to meet potential legal liabilities

Note: References in this question to NHS indemnity schemes include equivalent schemes provided by Health and Personal Social Services (HPSS) in Northern Ireland.

A35-1. 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*?

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

○ NHS indemnity scheme will apply
◉ Other insurance or indemnity arrangements will apply (give details below)

This project is part of Swansea University educational qualification and therefore, they will act as sponsor and provide indemnity cover (see attached documents).

Please enclose a copy of relevant documents.

A35-2. 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*?

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), describe the arrangements and provide evidence.

○ NHS indemnity scheme will apply to all protocol authors
◉ Other insurance or indemnity arrangements will apply (give details below)

This project is part of Swansea University educational qualification and therefore, they will act as sponsor and provide indemnity cover (see attached documents).

Please enclose a copy of relevant documents.

A35-3. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of *investigators/collaborators* and, where applicable, *Site Management Organisations*, arising from harm to participants in the *conduct of the research*?

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

◉ All participants will be recruited at NHS sites and NHS indemnity scheme or professional indemnity will apply
○ Research includes non-NHS sites (give details of insurance/indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A36. 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

If Yes, give details of the compensation policy:

This project is part of Swansea University educational qualification and therefore, they will act as sponsor and provide indemnity cover (see attached documents).

Please enclose a copy of relevant documents.

A37. How is it intended the results of the study will be reported and disseminated? *(Tick as appropriate)*

- [x] Peer reviewed scientific journals
- [x] Internal report
- [x] Conference presentation
- [ ] 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
- [x] Written feedback to research participants
- [ ] Presentation to participants or relevant community groups
- [ ] Other/none e.g. Cochrane Review, University Library

A38. How will the results of research be made available to research participants and communities from which they are drawn?

Research participants will receive a copy of the extended summary of the research findings and a copy will be supplied to a patient representation group, i.e. Arthritis Care so that all people living with OA knee will be informed of the outcomes.

A39. Will the research involve any of the following activities at any stage (including identification of potential research participants)? *(Tick as appropriate)*

- [ ] Examination of medical records by those outside the NHS, or within the NHS by those who would not normally have access
- [ ] Electronic transfer by magnetic or optical media, e-mail or computer networks
- [ ] Sharing of data with other organisations
- [ ] Export of data outside the European Union
- [x] Use of personal addresses, postcodes, faxes, e-mails or telephone numbers
- [ ] Publication of direct quotations from respondents
- [ ] Publication of data that might allow identification of individuals
- [ ] Use of audio/visual recording devices
- [x] Storage of personal data on any of the following:
  - [ ] Manual files including X-rays
  - [ ] NHS computers
  - [ ] Home or other personal computers
  - [x] University computers
  - [ ] Private company computers
  - [ ] Laptop computers

Further details:

All information gathered from this study will be held on a password protected University computer.

A40. What measures have been put in place to ensure confidentiality of personal data? Give details of whether any encryption or other anonymisation procedures have been used and at what stage:

On recruitment, participant details will be allocated a number. Patient details will only be accessible by the researchers involved.

A41. Where will the analysis of the data from the study take place and by whom will it be undertaken?

Analysis of data will take place in Swansea University by the chief investigator.

A42. Who will have control of and act as the custodian for the data generated by the study?

As the study is part of an educational project, chief custodian will be the supervisor working alongside the chief investigator.

A43. Who will have access to research participants' or potential research participants' health records or other personal information? *Where access is by individuals outside the normal clinical team, justify and say whether consent will be sought.*

N/A

A44. For how long will data from the study be stored?

10 Years Months

Give details of where they will be stored, who will have access and the custodial arrangements for the data:

Data will be stored in an electronic archive which is password protected held on a password protected computer at Swansea University. Data will be held in accordance with the Data protection act 1998

A45–1. 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

A45–2. 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

In all cases 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:
Dr	Gareth	Noble

Department: School of Health Science
Institution: Swansea University
Work Address: Swansea University
Glyndwr Building
Singleton Park, Swansea
Postcode: SA2 8PP
Telephone: 01792602026
Fax:
Mobile:
E-mail: j.g.noble@swansea.ac.uk

Please enclose a copy of any available comments or reports from a statistician.

Question(s) 46-47 disabled.

A48. What is the primary outcome measure for the study?

WOMAC Scale

A49. What are the secondary outcome measures? *(if any)*

Knee Range of Movement, Numerical Rating scale for pain.

A50. How many participants will be recruited?
If there is more than one group, state how many participants will be recruited in each group. For international studies, say how many participants will be recruited in the UK and in total.

Three groups of twelve participants. Therefore 36 participants in total.

A51. How was the number of participants decided upon?

Due the limitation in the amount of previously published research in the area of combined exercise therapy and interferential therapy; this research project is designed to be a feasbility based study, as described by the Medical Research Council. Feasibility studies, pilot studies and phase II trials are viewed as preparatory studies essential for determining the most appropriate questions for the next generation of phase III trials. Therefore, we are testing the protocol in order to generate the information needed to complete a sample size calculation for the next phase of the clinical study.

If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.

A52. Will participants be allocated to groups at random?

◉ Yes ○ No

If yes, give details of the intended method of randomisation:

A randomisation list will be generated on participants inclusion in the study. Patient details will be allocated to a number on inclusion to the study. Numbers 1–36 will be placed in an envelope and randomly assigned to a treatment group.

A53. 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 primary analysis for this study is to examine 'cause and effect' by comparing each of the experimental groups individually to the control. In this research design, each of the participants in the separate experimental groups will be the same participant, thus making this a same–subject design. The statistical analysis for this would either be McNemar for ordinal level data, (e.g. Quality of Life) and for the interval/ratio level data, (eg. Range of Movement) it would be the Wilcoxon test (if the data is considered non–parametric) or the related t test (if considered parametric). In order for an overal comparison between all groups, an One–way ANVOA with appropriate post–hoc tests will be utilised due to the comparisons of groups consisting of different participants.

A54. Where will the research take place? *(Tick as appropriate)*

- [x] UK
- [ ] Other states in European Union
- [ ] Other countries in European Economic Area
- [ ] Other

If Other, give details:

A55. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK, the European Union or the European Economic Area?

○ Yes ◉ No

A56. In how many and what type of host organisations (NHS or other) in the UK is it intended the proposed study will take place?

Indicate the type of organisation by ticking the box and give approximate numbers if known:

	Number of organisations
[x] Acute teaching NHS Trusts	1
[ ] Acute NHS Trusts	
[ ] NHS Primary Care Trusts or Local Health Boards in Wales	
[ ] NHS Trusts providing mental healthcare	
[ ] NHS Health Boards in Scotland	
[ ] HPSS Trusts in Northern Ireland	
[ ] GP Practices	
[ ] NHS Care Trusts	
[ ] Social care organisations	
[ ] Prisons	
[ ] Independent hospitals	
[ ] Educational establishments	
[ ] Independent research units	

☐ Other (give details)

Other:

A57. What arrangements are in place for monitoring and auditing the conduct of the research?

Swansea University, by acting as sponsor has a monitoring and auditing procedure for all post graduate research via the research student committee.

A57a. Will a data monitoring committee be convened?

○ Yes ◉ No

If Yes, details of membership of the data monitoring committee (DMC), its standard operating procedures and summaries of reports of interim analyses to the DMC must be forwarded to the NHS Research Ethics Committee which gives a favourable opinion of the study.

What are the criteria for electively stopping the trial or other research prematurely?

A58. Has external funding for the research been secured?

◉ Yes ○ No

If Yes, give details of funding organisation(s) and amount secured and duration:

Organisation:	Swansea University
Address:	Singleton Park Swansea
Post Code:	SA2 8PP
UK contact:	Deborah Fitzsimions
Telephone:	01792 518531
Fax:	
Mobile:	
E-mail:	
Amount (£):	2240 Duration: 18 Months

A59. Has the funder of the research agreed to act as sponsor as set out in the Research Governance Framework?

◉ Yes ○ No

Has the employer of the Chief Investigator agreed to act as sponsor of the research?

◉ Yes ○ No

Lead sponsor *(must be completed in all cases)*

Name of organisation which will act as the lead sponsor for the research:

Swansea University

Status:

○ NHS or HPSS care organisation ◉ Academic ○ Pharmaceutical industry ○ Medical device industry ○ Other

If Other, please specify:

Address:	Swansea University, Singleton Park, Swansea
Post Code:	SA2 8PP
Telephone:	01792205678
Fax:	+44 (0) 1792 295157
Mobile:	
E-mail:	

Sponsor's UK contact point for correspondence with the main REC *(must be completed in all cases)*

Title: Dr Forename/Initials: Gareth Surname: Noble

Work Address:	Swansea University Glyndwr Building Singleton Park, Swansea
Post Code:	SA2 8PP
Telephone:	01792 602026
Fax:	
Mobile:	
E-mail:	j.g.noble@swansea.ac.uk

Co-sponsors

Are there any co-sponsors for this research?

○ Yes ◉ No

A60. Has any responsibility for the research been delegated to a subcontractor?

○ Yes ◉ No

A61. Will individual *researchers* receive any personal payment over and above normal salary for undertaking this research?

○ Yes ◉ No

A62. Will individual *researchers* receive any other benefits or incentives for taking part in this research?

○ Yes ◉ No

A63. Will the host organisation or the researcher's department(s) or institution(s) receive any payment or benefits in excess of the costs of undertaking the research?

○ Yes ◉ No

A64. 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

A65. Research reference numbers: *(give any relevant references for your study):*

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

A66. Other key investigators/collaborators *(all grant co-applicants or protocol co-authors should be listed)*

Title: Forename/Initials: Surname:

Post:
Qualifications:
Organisation:
Work Address:

Postcode:
Telephone:
Fax:
Mobile:
E-mail:

A67. 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.*

On completion of the research, participants will be offered conventional physiotherapy within Abertawe Bro-Morgannwg University Trust.

A68. Overview of the research

To provide all the information required by the REC, 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.

A68–1. Lay summary. *Please provide a brief summary of the research (maximum 300 words) in lay language. This summary will be published on the website of the National Research Ethics Service following the ethical review.*

Osteo–Arthritis (OA) of the knee is a very common musculo–skeletal disorder suffered by millions of people throughout the world. The most common type of OA is that affecting the knee. Treatment includes the use of medication, physiotherapy and surgery. Physiotherapy treatment is a common form of treatment used to treat OA of the knee. Two commonly used treatment techniques used by physiotherapists are exercise therapy and a type of treatment called Interferential therapy (IFT). IFT uses electrical impulses to block pain transmission in the painful joint. The evidence behind the use of exercise therapy to treat OA Knee is fairly substantial, however the research behind the use of IFT is fairly limited, and research supporting the use of combined exercise therapy and IFT is even more sparse. The aim of this pilot study is to assess the effectiveness of the combined use of exercise therapy and IFT in the treatment of OA knee. The effectiveness of the treatments will be evaluated using commonly used outcome measures. Patients will undergo three weeks of treatment, with outcome measures being taken before and after the treatment intervention.
It is hoped that the results of this study will drive future treatment protocols and add to the body of research supporting the use of combination therapies.

A68–2. Summary of main issues. *Please summarise the main ethical and design issues arising from the study and say how you have addressed them.*

If participants percieve a benefit of treatment, participants will be offered extended treatment on completion of the study.

Question(s) 69 disabled.

A70. Give details of the educational course or degree for which this research is being undertaken:

Name of student:

Craig Dyson

Name and level of course/degree:

MPhil

Name of educational establishment:

School of Health Sciences, Swansea University

Name and contact details of educational supervisor:

Dr Gareth Noble,
Glyndwr Building,
Singleton Park,
Swansea University,
Swansea,
SA2 8PP

A71. Declaration of educational supervisor

I have read and approved both the research proposal and this application for the ethical review. I am satisfied that the scientific content of the research is satisfactory for an educational qualification at this level. I undertake to fulfil the responsibilities of a supervisor as set out in the Research Governance Framework for Health and Social Care.

Signature: .....

Print Name:

Date: (dd/mm/yyyy)

A one-page summary of the supervisor's CV should be submitted with the application

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 of which the main REC has given a favourable opinion and any conditions set out by the main REC in giving its favourable opinion.
4. I undertake to seek an ethical opinion from the main REC before implementing substantial amendments to the protocol or to the terms of the full application of which the main REC has given a favourable opinion.
5. I undertake to submit annual progress reports setting out the progress of the research.
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.
7. I understand that research records/data may be subject to inspection for audit purposes if required in future.
8. I understand that personal data about me as a researcher in this application will be held by the relevant RECs and their operational managers and that this will be managed according to the principles established in the Data Protection Act.
9. I understand that the information contained in this application, any supporting documentation and all correspondence with NHS Research Ethics Committees or their operational managers relating to the application:

   – Will be held by the main REC until at least 3 years after the end of the study.

   – May be disclosed to the operational managers or the appointing body for the REC in order to check that the application has been processed correctly or to investigate any complaint.

   – May be seen by auditors appointed by the National Research Ethics Service to undertake accreditation of the REC.

   – 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 lay summary of this study will be published on the website of the National Research Ethics Service (NRES) as it appears 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.

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.

Signature: .....

Print Name:

Date: (dd/mm/yyyy)

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 sponsor nominated to take the lead for the REC application.

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 A35, will be in place before this research starts.
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 NHS Research Governance Framework for Health and Social Care will be undertaken in relation to this research.**
7. I understand that the lay summary of this study will be published on the website of the National Research Ethics Service (NRES) as it appears 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.

* Not applicable to student research (except doctoral research).
** Not applicable to research outside the scope of the Research Governance Framework.

Signature: .....

Print Name:

Post:

Organisation:

Date: (dd/mm/yyyy)

Does this application relate to a research site for which the NHS (or HPSS in Northern Ireland) is responsible or to a non-NHS research site?

- (•) NHS site
- ( ) Non-NHS site

For HPSS sites in Northern Ireland, separate arrangements are in place for R&D applications. There is no need to complete questions marked "R&D only" on this form.

This question must be completed before proceeding. The filter will customise the form, disabling questions which are not relevant to this application.

In which country is the research site located?

- ( ) England
- (•) Wales
- ( ) Scotland
- ( ) Northern Ireland

The data in this box is populated from Part A:

Short title and version number:
Assessing the effect of Exercise Therapy and IFT on OA Knee

Name of NHS Research Ethics Committee to which application for ethical review is being made:

Project reference number from above REC: 08/WMW02/76

Name of NHS care organisation to which application is being made for permission to conduct the research:

NHS organisation reference (for R&D office use only):

1. Title of the research *(populated from A1)*

Full title: Assessing the effect of Exercise Therapy and Interferential Therapy on OA Knee: A feasability study.

Key words:
Osteoarthritis
OA
Arthritis
Exercise
Exercise Therapy
Rehabilitation
Active Rehabilitation
Physical Therapy
Physiotherapy
Physical Activity
Electrotherapy
Electrical Stimulation
TENS

IFT
US
Ultrasound
PSWD
Knee OA

2. Name of Chief Investigator *(populated from A2)*

Title:	Forename/Initials:	Surname:
Mr	Jonathan C	Dyson

3. Name of organisation acting as lead sponsor for the study *(populated from A59)*

Swansea University

4. Research reference numbers if known *(populated from A65)*

Applicant's/organisation's own reference number, e.g. R&D:

Sponsor's/protocol number:

Funder's reference number:

International Standard Randomized Controlled Trial Number (ISRCTN):

ClinicalTrials.gov Identifier (NCT number):

Project website:

6. Give the name of the NHS site within or through which the research will take place under the responsibility of the PI or Local Collaborator. *Please give the name only. Further details of locations should be given in question 8. The name of the site is normally the name of the relevant NHS organisation. Each NHS general or dental practice is a separate site unless a formal consortium/network is in place.*

Abertawe Bro-Morgannwg University Health Trust

Is this a primary care site?

○ Yes ◉ No

If Yes, give the name of the primary care organisation responsible for the site below:

8. Specify all locations, departments, groups or units at which or through which research procedures will be conducted at this site and describe the activity that will take place.

List all locations/departments etc where research procedures will be conducted within the NHS organisation, describing the involvement in a few words. Where access to specific facilities will be required these should also be listed for each location.

Name the main location/department first. Include details of any centres at other NHS organisations where potential participants may be seen or referred for inclusion in the research at this site. Give details of any research procedures to be carried out off site, for example in participants' homes.

	Location	Activity/facilities
1	Physiotherapy Department, Singleton Hospital, Sketty Lane, Swansea, SA2 8QA	Physiotherapy Department. All equipment needed for the study is available at the location. Data collection to take place at this site.

2		

12. Who is the Principal Investigator or Local Collaborator for this research at this site?

Title:	Forename/Initials:	Surname:
Mr	P	Dowdeswell

Post: Physiotherapy Manager

Qualifications:

Organisation: Abertawe Bro-Morgannwg University Health Trust

Work Address: Physiotherapy Department, Singleton Hospital

Sketty Lane

Swansea

Postcode: SA2 8QA

Telephone: 01792 285383

Fax:

Mobile:

E-mail:

	R&D Only
a) Will this person interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care?	○ Yes ◉ No
b) Does this person hold a current substantive or honorary contract with the NHS organisation or accepted by the NHS organisation?	◉ Yes ○ No

Please provide a copy of the c.v. for the PI.

If an honorary contract is held, a copy of the contract should be submitted, unless previously provided to the R&D office.

14. Give details of all other members of the research team at this site, including academic supervisors and all people who will interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care.

1. Research Member

Title:	Forename/Initials:	Surname:
Mr	Ron	Van Heeswijk

Employing organisation: Abertawe Bro-Morgannwg University Health Trust

Post: Physiotherapist

Qualifications:

Role in research team: researcher

	R&D Only
a) Will this person interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care?	○ Yes ◉ No
b) Does this person hold a current substantive or honorary contract with the NHS organisation or accepted by the NHS organisation?	◉ Yes ○ No

Please provide a copy of the c.v. for the research team member.

If an honorary contract is held, a copy of the contract should be submitted, unless previously provided to the R&D

office.

15. Does the Principal Investigator or any other member of the site research team have any direct personal involvement (e.g. financial, share-holding, personal relationship etc) in the organisation sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

If Yes, give further details:

16. What is the proposed local start and end date for the research at this site?

Start date: *(dd/mm/yyyy)*
Duration (Months):
End date: *(dd/mm/yyyy)*

17. Summary of the research *(populated from A10-1)*

The purpose of the planned study is to see whether the combination of exercise therapy and interferential therapy is more beneficial than either intervention alone when treating patient with osteo-arthritis of the knee.

It is planned to take thirty-six subjects, aged 45-70 all suffering with Osteo-arthritis (OA) of the knee who will be recruited from specialist GP clinics and consultant clinics around Abertawe Bro-Morgannwg University NHS Trust. Subjects will have been referred into these clinics by their GP.

Inclusion Criteria are as follows:
1. Age 45-70
2. Confirmed osteo-arthritis (OA) of the knee by way of radiological investigation (X-Ray).
3. Osteo-arthritis as defined by (Altman 1986), i.e. the patient experiences pain and any five of the following:
1. Over 50 years of age,
2. Less than 30 minutes of morning stiffness,
3. Crepitus (noisy, grating sound) on active motion,
4. Bony tenderness,
5. Bony enlargement,
6. No palpable warmth of synovium,
7. Erythrocyte sedimentation rate (ESR) less than 40 mm/hr,
8. Rheumatoid factor less than 1:40 titer (agglutination method),
9. Synovial fluid signs.

Patients will be excluded from the study if they:

1. Have had any other treatment in the previous six weeks
2. Have any other medical condition which could explain their current complaints.
3. Have Kellgren Grade IV OA (large osteophytes (bony growths), marked joint space narrowing, severe sclerosis (hardening of the cartilage) and definite deformity of bone ends. This is applied when X-Ray shows a very high level of OA presence)(Kellgren 1957).
4. Are primarily suffering with patello-femoral joint OA (Osteo-arthritis of another joint)
5. Are contra-indicated for exercise treatment or Interferential Treatment (IFT). Contraindications for IFT are as follows: Patients whose skin are easily damaged or bruised, patients who are on anti-coagulation therapy, patients with pacemakers, patients who have active malignancy. Contraindications to exercise therapy are as follows: Any uncontrolled cardiac conditions(aortic stenosis,cardiac enlargement,dysrhythmias,ventricular aneurysm,cardiomyopathy,congestive heart failure) or uncontrolled metabolic disorders (Diabetes, thyrotoxicosis, myxedema.)
6. Are unable to read and understand English.

Procedure

Patients will be assessed for their suitability for the study in the GP/consultant clinic. If suitable, subjects will be given an information sheet about the study see attached). The information sheet will contain details of the investigation and

state that they have the right to withdraw from the study at any time. The information sheet will also contain the contact details of the Chief Investigator. Subjects will be instructed to contact the Chief investigator if they wish to be included in the study. On contact with the Chief Investigator, patient name and contact details will be taken, and these details will be allocated to a number for randomisation. An appointment will be made to meet a physiotherapist who will act as the assessor of patient outcome. The physiotherapist will be blinded to the patient treatment. Informed consent will be obtained via a consent form issued prior to the start of the data collection process by the blinded physiotherapist. The blinded physiotherapist will carry out the following outcome measures during the initial assessment:

1. WOMAC Scale which consists of 24 questions, each corresponding to a visual analogue scale, designed to measure patients perceptions' of pain, stiffness and dysfunction.
2. Numerical Rating Scale (NRS) pain score. This is a numerical rating scale between 0–10. The patient is asked to rate their current pain on a scale of 0–10 with 0 meaning no pain and 10 meaning the worst pain imaginable.
3. Range of Movement. This will be a measurement of the patients knee flexion and extension by the blinded physiotherapist.

This collection of data should take 20 minutes.

Following collection of the data, patients will be given another appointment three weeks following the initial assessment. This three week period will act as the control period. After three weeks, patients will again be assessed by the same blinded physiotherapist using the same outcome measures, and will commence the treatment procedure that they will have been randomly allocated.

Patients will be randomly allocated into one of three groups:

1. Interferential Therapy only group
2. Exercise Therapy only Group
3. Combined therapy group

IFT Group

Patients in the IFT group will receive IFT twice a week, for three weeks, i.e. six sessions in total. Each session will last for twenty–five minutes and IFT will be concentrated on the painful knee. Standardized IFT stimulation parameters for pain relief will be used: carrier frequency 3.85kHz; 80–120Hz sweep; pulse duration 130¼s. Four electrodes will be placed around the knee joint so as to concentrate the effect of the IFT into the centre of the joint and will be attached via a velcro strap to ensure maximum skin contact.
IFT will be administered by the chief investigator.

Exercise Therapy Group

Patients in the exercise therapy group will also be treated twice a week for twenty minutes. The session will be broken up into the following format:
1. Warm up using static exercise bike x 3min at slow pace.
2. 6 exercise stations. Patient to exercise at each station for 40sec with 30 sec for change of station. Patient to complete circuit 3 times.
3. Warm down using static bike x 3min at slow pace
For example, each patient will do a warm up followed by the following circuit three times. After doing the circuit three times the patient will do the warm down.
Participants will carryout the following commonly used exercises:
1. Inner Range Quads in long sitting (sitting with legs on plinth and contracting thigh muscle).
2. Single Leg Balance. (Balancing on one leg)
3. Straight Leg Raise (sitting with legs on plinth and, keeping the leg straight, lifting the leg 2–3" off the bed).
4. Step Up Exercise (stepping up onto a step)
5. Passive Knee Flexion (the participant pulls their knee into a bent position)
6. Hamstring Curl (the participant lies on their front and bends their knee against gravity).
Patients in the Exercise group will be supervised by the chief investigator. Patients will be encouraged to continue with the exercises at home.

Combined Group

Patients in the IFT and Exercise group will do the above exercise regime and then receive 25 minutes of IFT set at the above parameters.

Control Group

Patients will act as their own control as they will be assessed following initial recruitment, wait three weeks to simulate a control period, then be assessed again prior to starting the treatment. For any patients complaining of increased symptoms following an exercise period, their exercise protocol would be modified accordingly on the opinion of the supervising physiotherapist.
Following completion of the study, patients will be offered conventional physiotherapy.
The second set of outcome measures will be recorded at least 48 hours after the last set of exercises to allow for any post-exercise stiffness.

Patients will be advised to continue using any medication prescribed prior to the start of the study, but will be excluded if any changes in analgesic medication occur during the study.
Patient name and contact details will be allocated to a reference number on allocation to the study. This data will be stored on password controlled university computers at Swansea University. This data will only be accessed by the Chief investigator and the research team. All assessment data recorded during the study will be kept in a sealed container in a lockable cabinet in Singleton Hospital. This will be accessed by the blinded physiotherapist carrying out the assessment, and the Chief investigator. Following completion of the study, all data will be stored at Swansea University for 10 years in compliance with the Data Protection Act 1998.

18. Details of clinical interventions *(populated from A12 where enabled)*

Additional Intervention	Average number per participant		Average time taken	Details of additional intervention or procedure, who will undertake it, and what training they have received.
	Routine Care	Research		
Other	0	6	25mins	Intervention is exercise therapy to be delivered over 6 stations, each lasting for 40seconds per station. Participants will exercise at each station 3 times per session and do 2 sessions per week over 3 weeks.Therefore the total treatment time will be 150mins.
Other	0	6	25mins	Interferential Therapy (IFT) which will be delivered for 25minutes, twice a week over three weeks. Therefore total treatment time will be 150mins

19. Details of non-clinical interventions *(populated from A13 where enabled)*

Additional Intervention	Average number per participant	Anticipated average time taken	Details of additional intervention or procedure, who will undertake it, and what training they have received.

20. Will any aspects of the research at this site be conducted in a different way to that described in Parts A and B or the study protocol?

○ Yes ◉ No

If Yes, explain and give reasons.

21. How many research participants/samples is it expected will be recruited/obtained from this site?

22. Give details of how potential participants will be identified locally and who will be making the first approach to them to take part in the study?

23. Who will be responsible for obtaining informed consent at this site? What expertise and training do these persons have in obtaining consent for research purposes?

1 ☐	Mr P Dowdeswell	
2 ☐	Mr Ron Van Heeswijk	

27. Is there a contact point where potential participants can seek independent advice about participating in the study?

R&D Only

28. Please provide a copy on headed paper of the participant information sheet and consent form that will be used locally. *This must be the same generic version submitted to/approved by the main REC for the study while including relevant local information about the site, investigator and contact points for participants (see guidance notes).*

If you consider that changes should be made to the generic content of the information sheet to reflect site-specific issues in the conduct of the study (see 20), give details below. A substantial amendment may need to be discussed with the Chief Investigator and submitted to the main REC.

29. What arrangements have been made for participants 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 etc.) (Populated from A29)*

Patients who do not understand English will be excluded from the study.
What local arrangements have been made to meet these requirements (where applicable)?

30. What arrangements will be made to inform the GP or other health care professionals responsible for the care of the participants?

33. What arrangements (e.g. facilities, staffing, psychosocial support, emergency procedures) will be in place at the site, where appropriate, to minimise the risks to participants and staff and deal with the consequences of any harm?

R&D Only

35. What are the arrangements for the supervision of the conduct of the research at this site? *Give name and contact details of any supervisor not already listed in the application.*

R&D Only

37. Will any external funding be provided for the research at this site?

○ Yes ◉ No

If Yes, indicate the source and details of the funding:

R&D Only

38. Which organisation will receive and manage this funding?

R&D Only

39. Authorisations required prior to R&D approval

This section deals with authorisations by managers within the NHS organisation. It should be signed in accordance with the guidance provided by the NHS organisation. This may include authorisation by line managers, service managers, support department managers, pharmacy, data protection officers or finance managers, depending on the nature of the research. Managers completing this section should confirm in the text what the authorisation means, in accordance with the guidance provided by the NHS organisation. This section may also be used by university employers or research staff to provide authorisation to NHS organisations, in accordance with guidance from the university.

Declaration by Principal Investigator or Local Collaborator

1. The information in this form is accurate to the best of my knowledge and I take full responsibility for it.
2. I undertake to abide by the ethical principles underpinning the World Medical Association's Declaration of Helsinki and relevant good practice guidelines in the conduct of research.
3. If the research is approved by the main REC and NHS organisation, I undertake to adhere to the study protocol, the terms of the application of which the main REC has given a favourable opinion and the conditions requested by the NHS organisation, and to inform the NHS organisation within local timelines of any subsequent amendments to the protocol.
4. If the research is approved, I undertake to abide by the principles of the Research Governance Framework for Health and Social Care.
5. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to the conduct of research.
6. I undertake to disclose any conflicts of interest that may arise during the course of this research, and take responsibility for ensuring that all staff involved in the research are aware of their responsibilities to disclose conflicts of interest.
7. I understand and agree that study files, documents, research records and data may be subject to inspection by the NHS organisation, the sponsor or an independent body for monitoring, audit and inspection purposes.
8. I take responsibility for ensuring that staff involved in the research at this site hold appropriate contracts for the duration of the research, are familiar with the Research Governance Framework, the NHS organisation's Data Protection Policy and all other relevant policies and guidelines, and are appropriately trained and experienced.
9. I undertake to complete any interim and/or final reports as requested by the NHS organisation and understand that continuation of permission to conduct research within the NHS organisation is dependent on satisfactory completion of such reports.
10. I undertake to maintain a project file for this research in accordance with the NHS organisation's policy.
11. I take responsibility for ensuring that all serious adverse events are handled within the NHS organisation's policy for reporting and handling of adverse events.
12. I understand that information relating to this research, and about me as a researcher, will be held by the R&D office and 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.
13. I understand that the information contained in this application, any supporting documentation and all correspondence with the R&D office and/or the REC system relating to the application 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.
14. I understand that information relating to this research (including my contact details) may be publicly available through the National Research Register.

Signature of Principal Investigator or Local Collaborator: .....

Print Name:

Date: