A systematic review on the effectiveness of manipulation and mobilisation in the treatment of osteoarthritis

By

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I, Ahmed Khamissa, do declare that this dissertation is representative of my own work in both conception and execution (except where acknowledgements indicate to the contrary).

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DEDICATION

I dedicate this dissertation to my family.

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ABSTRACT

Background: Osteoarthritis (OA) is an increasing condition globally as the population ages and the number of elderly increases. However, there is a lack of relevant evidence-based guidelines for manual therapy in the treatment of OA especially involving OA of the spine, wrist, temporomandibular joint (TMJ), and the glenohumeral joint (GHJ). A systematic review organises and critiques literature in a more concise form for practitioners. This study aimed to briefly provide practitioners the evidence available on the effectiveness of manipulation and mobilisation on OA.

Methods: A systematic review of available literature was performed using keywords including “manipulation”; “mobilization”; “manual therapy” and “osteoarthritis”; “spondylosis”; “degenerative joint disease”; “degenerative disc disease”. The database searches were through CINAHL, DUT summons, Google scholar, Pubmed and Scopus. Following a screening using inclusion criteria, 20 articles were chosen for review. Each of the studies were than reviewed by three reviewers using the Newcastle-Ottawa scale, the PEDRO scale, the Joanna Briggs Institute (JBI) scale for case series and the JBI scale for case reports. These scales evaluated the methodological rigour (internal validity) of the chosen articles. In addition, the external validity was determined through a critique of each article. The internal and external validity formed the basis for decisions on the level of evidence provided in support of manual therapy.

Results: Of those chosen articles, 13 provided evidence of treatment programmes and could not contribute to evidence specific to mobilisation and manipulation. In contrast, four articles assessed the efficacy of mobilisation, one study assessed the efficacy of manipulation, and two studies assessed the efficacy of neural mobilisation.

There was moderate evidence in support of mobilisation on thumb carpometacarpal (CMC) OA, but only limited evidence in support of its use on cervical spine OA and no evidence in support of its use on lumbar spine OA, GHJ OA and TMJ OA. Manipulation was suggested to have moderate to limited evidence in support of its use on lumbar spine OA, but no evidence for cervical spine OA. Neural mobilisation was suggested to have limited evidence in support of its use for treating thumb CMC OA.

Conclusion: It was evident in this systematic review that there is limited evidence for mobilisation, manipulation and neural mobilisation. Further research is required to expand on the limited areas, as well as strengthen the current evidence for clinical use.

Key terms: Manipulation; mobilisation; manual therapy; osteoarthritis; spondylosis; systematic review.

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LIST OF ABBREVIATIONS

ACL:	Anterior cruciate ligament
ADL:	Activities of daily living
APUP:	Posterior anterior unilateral pressure
BDI:	Beck depression inventory
BMI:	Body mass index
CINAHL:	Cumulative Index to Nursing and Allied Health Literature
CMC:	Carpometacarpal
COR:	Cervical oscillatory rotation
CR:	Conventional rehabilitation
DJD:	Degenerative joint disease
FU:	Follow up
HVLA:	High velocity low amplitude
IFC:	Interferential current therapy
JBI:	Joanna Briggs Institute
JSTOR:	Journal storage
LBP:	Lower back pain
MILT:	Mechanical Intermittent lumbar traction
MM:	Mulligans mobilisation
MRI:	Magnetic resonance imaging
NDI:	Neck disability index
NOS:	Newcastle-Ottawa scale
NPS:	Numeric pain scale
nRCT:	Non-randomised controlled trial
NSAIDs:	Non-steroidal anti-inflammatory drugs
OA:	Osteoarthritis
ODI:	Oswestry disability index
PAUP:	Posterior anterior unilateral pressure
PNF:	Proprioceptive neuromuscular facilitation
PPT:	Pressure pain threshold
PSFS:	Patient specific functional scale
RCT:	Randomized controlled trial
ROM:	Range of motion
SLR:	Straight leg raise
SPADI:	Shoulder pain and disability index

STAI: State trait anxiety inventory

SWD: Short wave diathermy

TENS: Transcutaneous electrical nerve stimulation

TMJ: Temporomandibular Joint

TOP: Transverse oscillatory pressure

THR: Total hip replacement

TKR: Total knee replacement

VAS: Visual analog scale

WOMAC: Western Ontario and McMaster Universities arthritis index

LIST OF DEFINITIONS

Manipulation: A form of manual therapy, which involves high velocity, low amplitude thrusts applied to a joint. They are manoeuvres that induce joint motion through either mobilisation (non-thrust techniques) or manipulation (thrust techniques) (Bergmann and Petersen 2011; Cao *et al.* 2013). The thrust is delivered at the restrictive joint barrier or the direction of reduced joint motion to increase range and quality of motion, as well as decrease pain (Boff *et al.* 2020; Bergmann and Petersen 2011). Mintken *et al.* (2008) defined a manipulative technique using six characteristics: rate of force application; location in range of available movement; direction of force; target of force; relative structural movement, and patient position. An example of this would be a high velocity, end-range, posterior to anterior force to the mid thoracic spine in a prone position. Manipulation, as relating to mobilisation, is a grade 5 mobilisation where the technique is performed at such a speed that it does not allow the patient to prevent it. This gives it the description of a high velocity (very quick), low amplitude (low force) thrust performed at the end of an available range (Hengeveld and Banks 2005). Grades 1–4 will be discussed in the mobilisation definition. This study includes grade 5 mobilisation or manipulation.

Mobilisation: A form of manual therapy with multiple techniques, such as, mobilisation with movement and Maitland accessory glides (Hengeveld and Banks 2005). Mobilisation means passive or active movements performed in a manner and speed that are within the control of the patient and if the patient chooses so, they can prevent it (Hengeveld and Banks 2005). Most involve the stretching technique performed at or near the end of range of motion aiming to elongate connective tissue (Blackman and Atkins 2014; Hengeveld and Banks 2005). Grading of mobilisation is used to indicate the extent of the position chosen in the available range of motion and are graded numerically 1–5. Grade 1 is a small amplitude movement performed at the beginning of available range; Grade 2 is a larger amplitude movement performed within the resistance free part of available range; Grade 3 is a large amplitude movement performed up to the limit or resistance of available range; Grade 4 is a small amplitude movement performed into the end range or resistance of available range, and Grade 5 is high velocity, small amplitude movement performed at the

end of available range. Mobilisation lies within grade 1–4 (Hengeveld and Banks 2005). This study includes grades 1–4 mobilisation techniques.

Osteoarthritis: Osteoarthritis (OA) is the most common joint disease worldwide, affecting around 10% of men and 18% of women over 60 years of age (Glyn-Jones *et al*. 2015). It is a complex condition affecting the whole joint where activation of matrix proteases appears to have a major role (Glyn-Jones *et al*. 2015). Cartilage, subchondral bone, synovium and systemic inflammation all have a role in the disease pathogenesis (Glyn-Jones *et al*. 2015). OA is generally diagnosed with plain film radiography showing signs of joint space narrowing, osteophyte formation, subchondral sclerosis and cysts (Glyn-Jones *et al.* 2015; Taruc-Uy and Lynch 2013). Other signs and symptoms include deep pain, crepitus, effusion and decreased range of motion (Taruc-Uy and Lynch 2013). Magnetic resonance imaging (MRI) is also used as it is more sensitive in detecting early stages of OA. Many therapeutic strategies have been proposed but none have led to both symptom and structural changes to the condition (Glyn-Jones *et al.* 2015). For the purpose of this study, OA will be defined as degeneration of joint surfaces with bone remodelling and spur formation with symptoms of pain, and limited range of motion (Villafane 2013; Nicolakis *et al.* 2001). This includes spondylosis, characterised by spur formation, vertebral remodelling and degeneration of ligaments, intervertebral discs and facet joints and sometimes radiculopathy (Corpurgensli *et al.* 2017; Sokunbi 2015). This study is limited to all studies that do not include the knee and hip, as these have had extensive reviews completed (Anwar *et al.* 2018; Beumer *et al.* 2016; Ceballos-laita *et al.* 2019; Chen *et al*. 2018; Sampath *et al.* 2016). This study does include the spine, shoulder, wrist and temporomandibular joint.

Systematic review: Systematic reviews are known for their methodological rigor and are thus the reference standard for incorporating evidence in health care (Moher *et al.* 2015). Systematic reviews can be performed on all types of research, including randomised trials, cross-sectional studies, cohort studies and qualitative research (Clarke 2011). A systematic review attempts to collect all relevant studies to answer a specific research question. The evidence collected, based on a pre-specified eligibility criteria uses a systematic method to minimise bias where conclusions and decisions can be made from (Liberati *et al.* 2009; Clarke 2011). In this study, eligibility was based on the following key terms, “manual therapy”, “manipulation”, “mobilization”, “osteoarthritis”, “spondylosis”, “degenerative joint disease” and

"degenerative disc disease". The characteristics of a systematic review area clear set of objectives with a reproducible methodology, a systematic search that identifies all studies that meet the eligibility criteria, assessing the validity of each study, and lastly a presentation and incorporation of the findings from the included studies (Moher *et al.* 2015; Ahn and Kang 2018). The evidence is then synthesised, which may or may not include a meta-analysis dependent on study type inclusion (Clarke 2011). This study will be a systematic review without a meta-analysis because of the study type inclusion.

Meta-analysis: Using statistical techniques to summarise and combine the results of many studies this method of review can provide a more accurate estimate of the effect of the intervention through the review of a common clinical outcome measure, compared to a single study. This is mainly performed on randomised controlled trials because of their high level of evidence, their repeated measures and the likelihood for common clinical outcome measures (Moher *et al.* 2015; Ahn and Kang 2018). This is unlike a systematic review, which only collects, critically reviews methods and analyses the clinical outcomes of studies pertaining to certain topic (Ahn and Kang 2018). In contrast, a meta-analysis limits the inclusion of studies as the studies are required to have the same comparable outcome measures that have been recorded at similar time points in the treatment plan (McKenzie *et al.* 2016). This study is not a meta-analysis.

CHAPTER ONE INTRODUCTION

1.1 INTRODUCTION TO THE STUDY

Osteoarthritis (OA) is a condition that is described as the deformation of the articular cartilage, underlying bone and joint margins (Glyn-Jones *et al.* 2015; Goode *et al.* 2013). Most often the weight bearing joints are involved, leading to deep pain, worsened by movement, joint space narrowing, subchondral sclerosis, osteophytic growths and cysts (Taruc-Uy and Lynch 2013; Karsdal *et al.* 2016; Hunter and Bierma-Zeinstra 2019). Risk factors for degeneration of these anatomical structures include old age, obesity, bone or cartilage damage and joint biomechanical abnormalities caused by anatomical or functional factors (Glyn-Jones *et al.* 2015). The issue with osteoarthritis is that the symptoms display the disease when it is quite advanced and most probably irreversible (Glyn-Jones *et al.* 2015).

As a result, OA effects more than 40 million people in the United States. While, worldwide it effects roughly 18% of women and 10% of men over the age of 60 (Glyn-Jones *et al.* 2015, Taruc-Uy and Lynch 2013). By 65 years of age, roughly 80% of the population has some radiographic evidence of OA (Karsdal *et al.* 2016). Spinal OA is estimated to range from 40% to 85% (Goode *et al.* 2013).

Currently, direct costs include medication, surgery, clinic visits and an indirect cost of missed days of work (absenteeism), presenteeism and reduced productive activity related co-morbidities (Taruc-Uy and Lynch 2013). A much larger issue among the elderly is loss of independence and the need for increased support from others (Taruc-Uy and Lynch 2013; Hunter and Bierma-Zeinstra 2019). These concerns are likely to increase as the population ages and the elderly increase in number (Hunter and Bierma-Zeinstra 2019).

Treatments for OA currently include invasive (pharmacological, surgical) and non-invasive (life style changes and alternative care options). Pharmacological interventions, such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), are used for symptom control (Glyn-Jones *et al.* 2015) and disease modifying drugs for OA are used to limit joint destruction. The latter are under investigation but the majority have limited success or result in failure due to increasing side effects (Karsdal *et al.* 2016; Glyn-Jones *et al.* 2015). This means that at the very best these medications provide are a ‘hit-and-miss’ treatment where some patients benefit, others have significant side effects and others have no effect at all (Karsdal *et al.* 2016). This is further complicated by the findings of MacDonald *et al.* (2014),

who found that 66% of people with OA used non-prescription medication to manage symptoms (amid a myriad of co-existing conditions) and less than 25% saw a physiotherapist, occupational therapist or a pharmacist to manage the condition, leading to medication induced complications.

By comparison, surgical approaches are used to relieve pain and correct structure or when conservative approaches have failed, to address limitations to the activity of daily living. Thus, the short-term and long-term effectiveness of surgery are limited (Hunter and Bierma-Zeinstra 2019).

Joint replacement surgery, which is the most common treatment in OA of the knee, is considered cost effective if used for end-stage OA patients when all conservative approaches have failed and their quality of life is greatly reduced (Hunter and Bierma-Zeinstra 2019). In addition, up to 20% of total knee replacement (TKR) patients post-surgery gained little benefit or found a poor outcome (Price *et al.* 2018). Wylde *et al.* (2011) found that 44% of TKR and 27% of total hip replacement (THR) patients complained of post-surgical pain. Although most were mild in severity, 15% of TKR and 6% of THR patients reported severe-extreme post-surgical pain. Additionally, complications include venous thromboembolism, infection, neurovascular injury, prosthetic joint infection and wear and tear of the prosthesis. Furthermore, arthroscopic knee surgery, which is widely used for knee OA lacks evidence, and has shown to have minimal benefit and an obvious risk of harm (Hunter and Bierma-Zeinstra 2019). Similarly, for lumbar spinal stenosis (secondary to degeneration), the rate of side effect occurrence due to surgery ranged from 10% to 24%. Complications included lesions to the dural sac, neural dysfunction due to peridural haematoma, spinous process fracture and/or pulmonary oedema (Zaina *et al.* 2016).

In contrast, life style changes, including muscle strengthening, range of movement therapy, aerobic conditioning, occupational therapy, patella taping, weight loss, social support, walking aids, bracing, shock absorbent insoles, healthy eating habits and education, are available to assist patients with OA (Stevenson and Roach 2012; Carmona-Teres *et al.* 2015). It has been suggested that exercise (strength training and aerobic conditioning) reduces pain, improves physical function and quality of life, which is comparable NSAIDs (Fransen *et al.* 2015), without the attendant side effects and medication interactions.

In addition, alternative care may include acupuncture, physiotherapy modalities (e.g., transcutaneous electrical nerve stimulation, heat and cryotherapy), manipulation and mobilisation, which might be effective for symptom relief (Dwyer et al 2015; Evaniew and

Evaniew 2017; Mutlu *et al.* 2018; Hoeksma *et al.* 2004; Poulsen *et al.* 2013; Anwar *et al.* 2018). Several studies have found that specifically manual therapy, with or without exercise, or patient education may be beneficial in reducing pain, as well as increasing physical performance, range of motion and function, again without the attendant side effects of medication or surgery (Anwar *et al.* 2018; Hoeksma *et al.* 2004; Poulsen *et al.* 2013).

Therefore, it may be that the invasive treatment options have poor clinical outcomes, do not improve the quality of life of the patient and often have side effects. In contrast, non-invasive therapies may be able to improve the quality of life, avoid the side effects seen in invasive therapies and also be used as a precursor to improve outcomes of invasive interventions. However, little is known on the level of evidence in support of manual therapy for OA outside of the knee and the hip (Anwar *et al.* 2018; Beumer *et al.* 2016; Ceballos-laita *et al.* 2019; Chen at al. 2018; Sampath *et al.* 2016). This means that practitioners are recommending manual therapy in the treatment of spinal osteoarthritis based on limited evidence, which impacts on informed consent (Allied Health Professions Council of South Africa. 2001; Liberati *et al.* 2009; McQuoid-Mason and Dada 2011; Sampath *et al.* 2016; Anwar *et al.* 2018).

The best manner to address this challenge is through a systematic review, which aims to investigate the available evidence on manual therapy for OA on its effectiveness as a method of treatment, while also evaluating the level of evidence available (Moher *et al.* 2015; Liberati *et al.* 2009). A systematic review will state the level of evidence available on the chosen topic, as well as allow for better implementation in management strategies and reduce costs for the care of osteoarthritis (Kolasinski *et al.* 2020; Clijsters *et al.* 2014; Ceballos-laita *et al.* 2019)

1.2 AIM

The aim of this study was to investigate whether non-invasive manual therapies, in the form of mobilisation and manipulation, are effective or not in the treatment of osteoarthritis, by reviewing all research that investigated this, especially RCTs, non-randomised controlled trials, case studies and observational studies. Through this, a reliable breakdown of evidence will be available to health care practitioners on the treatment of osteoarthritis with non-invasive manual therapies.

1.3 OBJECTIVES

1. To determine the level of methodological rigour of studies investigating mobilisation and manipulation as a treatment for osteoarthritis.
2. To determine whether the use of mobilisation and manipulation as a treatment for osteoarthritis has a positive, negative or unequivocal clinical outcome.
3. To determine the level of evidence to support the use of mobilisation and manipulation as a treatment for osteoarthritis.
4. To make recommendations for further investigations and randomised controlled trails to improve investigations in respect of mobilisation and manipulation as a treatment for osteoarthritis.

1.4 RATIONALE AND BENEFITS OF THE STUDY

Treatments for OA generally include medication, surgery and conservative care. Non-steroidal anti-inflammatory drugs and subsequent arthroplastic surgery, however, have limitations and adverse long-term effects including decreased ability in activities of daily living (or ADLs), increased medical costs, and possible side effects (Glyn-Jones *et al.* 2015). In the same context, however, conservative care and physical activity have been shown to improve functionality and decrease pain (Fransen *et al.* 2015; Hoeksma *et al.* 2004). The limitation with manipulation and mobilisation is that the evidence for their use has not been made clear, effecting the ability to recommend manipulation and mobilisation for the treatment of OA. Guidelines are incomplete or refer to inadequate evidence, and the process of informed consent is limited (Sampath *et al.* 2016; McQuoid-Mason and Dada 2011).

Thus, these needs emphasise the importance of more research in this area (Goode *et al.* 2014; Taruc-Uy and Lynch, 2013). This is further enhanced by the fact that there is a significantly older population that is living longer (Goode et al. 2014) and who are more likely require care outside the realm of medication or surgery. Additionally, more patients are turning to conservative therapies as a first line of treatment (Tatalias, 2006; Phang *et al.* 2018).

A systematic review will assist in collecting the results of studies that are non-surgical and non-pharmacological (mobilisation and manipulation), to evaluate their clinical effectiveness so as to make recommendations for practice, which will assist in reducing risks and costs involved (Wylde *et al.* 2011). With a summary of all evidence available on manipulation and mobilisation, as well as the level of evidence of each study stated, improved guidelines can be made for the implementation of manual therapy in the treatment of OA (Liberati *et al.* 2009; Moher *et al.*

2009). A systematic review will also help recommend further research that needs to be done to further improve the evidence available on mobilisation and manipulation (Green 2005).

1.5 LIMITATIONS OF THIS SYSTEMATIC REVIEW

The limitations of this systematic review include the following:

- All non-English language articles were not included. It is, however, acknowledged that the exclusion of these article may have led to language bias, which would impact this systematic review in that the outcomes of the non-English studies may have had the ability to sway the level of evidence in favour of or against the use of manipulation and mobilisation in the treatment of OA of the spine (Hartling *et al.* 2017; Morrison *et al.* 2012; Egger *et al.* 2003). Systematic reviews relating to complementary and alternative medicine were found to be more likely impacted by the exclusion of non-English studies (Hartling *et al.* 2017; Morrison *et al.* 2012) Thus, future systematic reviews should include non-English studies which could either be translated/back translated to reduce bias or the use of multilingual reviewers could be used to review the articles to ensure their proper inclusion and review (Morrison *et al.* 2012).

- Given the nature of the scales used to rate the articles in this systematic review (PeDro scale 1999; Wells *et al.* 2003; JBI critical appraisal checklist 2017), these review scales have explanation notes to facilitate review processes; however, the level of research experience and/or literature critique can result in differences of interpretation of these scales and the attendant explanations by reviewers (Hartling *et al.* 2013; Higgins *et al.* 2011). This, therefore, has the potential to result in differences in the review of the articles (interpretation bias). One method would be to utilise training of the reviewers; however, this is not possible as a collective as the reviewers were required to submit blinded reviews (Hartling *et al.* 2013). Thus, this research utilised the option of an arbitrating reviewer in resolution of review discordance, as well as the possibility of a consultative meeting to facilitate a resolution of discrepancies.

- Although literature suggests that the inclusion of grey literature is supported (Blackhall 2007), there was no grey literature that met the inclusion criteria of this study.

- This study was not intended to be a meta-analysis but rather a systematic review. The limitations of a meta-analysis include the need for one outcome measure being consistent between included articles so that this outcome measure can be utilised as

pooled data for statistical analysis (Ahn and Kang 2018). Although this increases the data set, and therefore the strength of the conclusions drawn from a statistical basis, it can only include limited numbers of studies, does not provide a comprehensive overview of clinical outcomes, and cannot account for influences on the analysed clinical outcome. In contrast, a systematic review can include all clinical outcome measures and, therefore, provides a more comprehensive review of the impact of different interventions, but still suffers from the limitations that are inherent in the studies included in the systematic review (Ahn and Kang 2018).

1.6 CONTENT OF CHAPTERS

This chapter provided an introduction to the topic of manipulative and mobilisation as a treatment option for OA. The aim and objectives, as well as the rationale and limitations of the study were also included. Chapter Two explores the research problem through a literature review. Chapter Three describes the methodology of this systematic review. Chapter Four presents the results obtained from this study, followed by a discussion of these results in Chapter Five. Finally, a conclusion is drawn from a summary of the findings and recommendations for future research are given in Chapter Six.

CHAPTER TWO LITERATURE REVIEW

2.1 INTRODUCTION

This chapter provides a brief outline of osteoarthritis (OA), its epidemiology, pathophysiology, clinical features, the diagnosis, the impact of the clinic features and diagnosis, treatment and management of OA and the attendant prognosis. Finally, the chapter presents a brief description of systematic reviews, the role they play, their hierarchy in research, study biases and the specifics of systematic reviews of randomised controlled trials, non-randomised controlled trials, and observational studies.

2.2 A NORMAL JOINT

To facilitate a greater understanding of the changes that occur within a normal joint because of OA, it is essential to understand the relationship of the various structures and processes that maintain a normal joint. Additionally, it is important to review the normal aging process that occurs within a joint.

2.2.1 Normal Joint Anatomy and Physiology

OA generally affects joints that are classified as synovial joints. These joints are characterised by the following structural identifiers (Tortora and Derrickson 2009):

- Hyaline or articular cartilage.
- Two layered articular joint capsule.
- Joint cavity.
- Synovial membrane and synovial fluid.
- Supporting ligaments and muscles.

Synovial joints are classified in to six types based on the movement they allow (Moore *et al.* 2014; Tortora and Derrickson 2009):

1. The pivot joint (atlantoaxial joint), allowing rotation.
2. The plane joint (acromioclavicular joint), allowing gliding or sliding.
3. The ball and socket joint (hip), allowing movement in multiple axis.
4. The hinge joint (elbow) allowing movement in one plane, such as flexion and extension.
5. The saddle joint (carpometacarpal joint) allowing abduction, adduction, flexion and extension.

6. And the condyloid joint, also allowing flexion, extension, abduction and adduction (metacarpophalangeal joint).

Synovial joints are differentiated from other joints by the presence of the synovial cavity, which is a space between articulating bones. This joint allows free movement between the bones they join (Moore *et al.* 2014). In a synovial joint, the bones are covered in hyaline cartilage which reduces friction between bones due to it being smooth and slippery and can also aid in absorbing shock (Tortora and Derrickson 2009). Incapsulating the synovial joint is the articular joint capsule made up of the outer fibrous membrane and the inner synovial membrane. The outer fibrous layer attaches both articulating bones together, allows movement between them, while also preventing dislocation and keeps bones close together in a synovial joint.

The inner synovial membrane layer is made of up loose connective tissue, which in many joints also includes articular fat pads. The inner layer also secretes synovial fluid, which is a viscous fluid that coats the articulating surfaces with functions such as shock absorption, reducing friction, supplying nutrients and removing waste. It also contains phagocytic cells that remove debris and microbes resulting from the wear and tear of the joint (Tortora and Derrickson 2009). Changes within the synovial joint over time are thought to be the mechanism and cause of pain in OA, but the exact cause of pain is still mostly unknown and remains a mystery. However, there are multiple sources that seem to have an input in to the pain of OA. The main signifying change in OA is the continuous damage and repair of the articular joint, the loss of articular cartilage with simultaneous subchondral bone remodelling, osteophyte formation, joint space narrowing and synovitis (Fu *et al.* 2017; Woldin *et al.* 2014; Sofat *et al.* 2011).

Some studies have shown that bone marrow lesions, synovitis and joint effusion have a strong association with pain in OA, while cartilage damage has a weak association to pain (O'Neill and Felson 2018; Fu *et al.* 2017; Baker *et al.* 2010). Inflammation has also been studied as a factor in the development of OA pain, which then triggers changes in the joint due to the release of inflammatory mediators, further increasing pain (Fu *et al.* 2017). OA also leads to the formation of new vascular structures through angiogenesis, allowing the growth of new sensory nerve fibres, which has also been suggested as a further contribution to pain in OA (Ashraf *et al.* 2016).

Peripheral sensitization has been found to occur in inflammatory conditions where the sensory nerves innervating the joint capsule, synovium, ligaments, subchondral bone and periosteum (myelinated A delta and unmyelinated C fibres) become hyperexcitable, where even normally non harmful stimulation or mild damage can intensify pain within a joint (Fu *et al.* 2017). This

state can remain for weeks after inflammation has developed, as seen in OA, and is considered as another possible factor in OA pain (Fu *et al.* 2017).

Central sensitization involves changes in the processing of sensation within the spinal cord and brain. This occurs due to hypersensitivity of the nociceptive system by presenting with hyperalgesia, which is an increased sensitivity to noxious stimulus, or pain caused by a stimulus which is normally not harmful (allodynia) (Fu *et al.* 2017). The receptive field for pain can also expand, meaning the pain is more widespread, pain is located in more areas, and pain may also last longer (Girbes *et al.* 2016).

2.2.2 Normal Degenerative Process of Joints with Age

Osteoarthritis is a condition that affects the entire synovial joint, which includes the cartilage, subchondral bone, capsule, synovium, ligaments and periarticular muscles (Cope *et al.* 2019; Hunter and Bierma-Zeinstra 2019). Processes such as degeneration of cartilage, abnormal bone remodelling, and synovial inflammation are found to occur in OA (Cope *et al.* 2019; Glyn-Jones *et al.* 2015). The degeneration of cartilage occurs due to the action of proteolytic (breaks down protein) enzymes that degrade cartilage tissue constituents like proteoglycans and collagen (Abramson and Attur 2009).

The composition of cartilage changes which makes it easily affected by physical forces. First comes the erosions on the surface, followed by cartilage fissures that are deeper, and ultimately increased calcification (Hunter and Bierma-Zeinstra 2019). The abnormal bone remodelling is caused by an increase in the breakdown of cartilage and an inadequate reparative process which occurs with increasing age, rather than the previously thought of wear and tear theory (Hunter and Bierma-Zeinstra 2019; Abramson and Attur 2009).

Initially it was thought that the imbalanced degeneration and repair of cartilage is what occurs first in OA. However, the initiator of the process is unknown. One common theory is that when pro-inflammatory cytokines are secreted into the synovial joint, matrix metalloproteinases (MMPs) are triggered, leading to the degeneration and degradation of the cartilage, bone remodelling and synovitis (Cope *et al.* 2019; Glyn-Jones *et al.* 2015). MMPs are in charge of degrading proteins in the extracellular environment and play an important role in in the development of tissue, tissue repair, injury healing and remodelling post-injury (Nagase *et al.* 2006).

Other studies have argued that synovitis and subchondral bone remodelling occur before articular degeneration takes place in the early stages of OA (Benito *et al.* 2005; Cucchiarini 2016; Cope 2019). As OA progresses and becomes more severe, osteophytes form along with subchondral sclerosis which occurs due to synovial inflammation, bone and cartilage repair and cartilage degeneration (Man *et al.* 2014).

2.2.2.1 Cartilage

At first, OA was thought to be a condition that only involved the mechanical degradation of cartilage but it is now known that it is a disease that affects the whole joint (Glyn-Jones 2015). Articular cartilage is mechanically less capable of taking tension or shear stresses at the edges of the joint contact areas, so high levels of tension or stress in these areas can predispose the cartilage to splitting or softening and the development of vertical clefts between chondrocytes known as fibrillation (Burr and Gallant 2012). Another predisposition for cartilage to deteriorate is area where the underlying subchondral bone stiffness and density is not equal to regions that are soft and transition regions which cause deformities in the overlying cartilage (Burr and Gallant 2012).

Ultimately, the cartilage loses it integrity which further increases the likelihood of being damaged by external forces. Erosions first start out on the surface, but then deeper fissures start to form leading to calcification of the cartilage (Hunter and Bierma-Zeinstra 2019). Hypertrophic chondrocytes attempt to repair the damage by increasing their synthetic activity but in this processes they also cause the release of proinflammatory cytokines that cause further imbalances in chondrocyte function and affect the adjacent synovium (Hunter and Bierma-Zeinstra 2019).

As mentioned above in Section 2.2.2, one of the possible theories for the worsening of OA are the proinflammatory cytokines released by the deteriorating cartilage into the synovial joint which triggers matrix metalloproteinases leading to further degradation of cartilage, bone remodelling and synovitis (Cope *et al.* 2019).

2.2.2.2 Synovium

Synovitis is a common feature seen in OA which is associated with the progression of OA. When synovitis occurs, synoviocytes are found to proliferate, the synovial membrane hypertrophies and there is an increase in vascularity (Hunter and Bierma-Zeinstra 2019; Glyn-Jones *et al.* 2015). Following damage to the joint, inflammatory mediators are released which

can activate chondrocytes and osteoblasts, further releasing more inflammatory mediators and degenerative enzymes, which continue the process of inflammation (Glyn-Jones *et al.* 2015). As OA progresses, pro-inflammatory and catabolic products are also released by the synovial membrane. These include agrecanases and metalloproteinases, which help in degrading the articular matrix (Scanzello and Goldring 2012). In another study, it has been suggested that the secretion of proinflammatory cytokines into the synovial joint triggers matrix metalloproteinases, which cause the destruction of cartilage leading to synovitis and bone remodelling (Cope *et al.* 2019). One study has found that the percentage of patients with synovitis seems to increase as the deterioration of OA progresses, where 38% of patients with stage 2-3 OA had infrapatellar synovitis, while 83% of those in stage 4 of the disease had synovitis (Kransnokutsky *et al.* 2011).

Synovial fluid contributes to the function of the articular surface, as well as the control of chondrocyte activity. Lubricin and hyaluronic acid (HA) are produced by synoviocytes, which are important in preserving the articular cartilage surfaces (Scanzello and Goldring 2012). They lubricate, reduce friction, and prevent proteins from being deposited in the articular surfaces but, in OA, their concentrations are altered (Hui *et al.* 2012; Scanzello and Goldring 2012). Due to the synovial membrane hyperplasia and inflammation occurring in OA, the membrane permeability changes which possibly assists in lowering the concentration of lubricin and HA seen in the synovial fluid (Scanzello and Goldring 2012).

2.2.2.3 Subchondral Bone

The subchondral bone (SCB) is found deep to the articular cartilage with a layer of calcified cartilage, also known as the subchondral bone plate, between them, connecting the two layers (Stewart and Kawcak 2018). The roles of the SCB include providing nutritional support to the articular cartilage, mechanical support by means of distributing loads across the joint, and preventing areas of concentrated stress, which protects the articular cartilage from damage (Stewart and Kawcak 2018; Wen 2014; Burr 2012). It has also been shown that the SCB is also a possible source of inflammatory mediators which can lead to degeneration of the deeper layers of the articular cartilage (Berenbaum 2013).

The SCB has recently become more widely studied relating to OA, as it has been found that changes to the structure of the subchondral bone seems to have some effect on the changes found in OA, such as when subchondral bone sclerosis occurs, the ability of the SCB to absorb shock reduces and the risk or articular cartilage damage increases (Stewart and Kawcak 2018). Moreover, the deterioration of the articular cartilage near the edges of the joint can also

be worsened by an imbalance in the density of some areas in the SCB, as it has been found that the articular cartilage tends to deform more in the areas where the SCB is less dense, versus the areas where the subchondral bone is denser (Burr and Gallant 2012). In those areas where there is an inconsistency in density, the articular cartilage is more likely to fail.
Early-stage OA is defined as the presence of both joint pain and minor radiographic changes, as well as cartilage or subchondral bone changes and lesions, which can be seen using MRI or performing an arthroscopy (Cucchiriani *et al.* 2016).

In this early stage, bone remodelling occurs, which can be due to the subchondral microfractures that occur, leading to the resorption of bone by osteoclast, followed by the formation of bone by osteoblasts (Cucchiriani *et al.* 2016). This bone remodelling occurs at a much higher rate than normal, which leads to a decrease in bone stiffness because of limited bone mineralisation (Goldring and Goldring 2010). New vascular structures then invade the subchondral bone, the subchondral bone plate and the articular cartilage. This bone restructuring has also been associated with subchondral bone marrow lesion development (Hunter and Bierma-Zeinstra 2019). However, in late stage OA, the opposite happens where bone remodelling decreases leading to an increased deposition of bone. This causes the subchondral bone and subchondral bone plate to thicken and increase in density, leading to subchondral sclerosis (Burr and Gallant 2012; Cucchiarini *et al.* 2016).

2.3 OSTEOARTHRITIS

2.3.1 Definition of OA

OA is a condition that involves mobile joints that undergo extracellular matrix degradation that start from joint macroinjury and leads to microinjury changes. This triggers abnormal repair and remodelling that include the activation of pro-inflammatory pathways (see Section 2.2.2). The condition begins as an alteration in tissue metabolism, which progressively leads to physiological and anatomical changes, such as articular cartilage damage, joint inflammation, bone remodelling and the formation of osteophytes (Kraus *et al.* 2015). Clinically, the disorder presents with joint pain, limited movement, tenderness, possible joint effusion, inflammation and crepitus (Kraus *et al.* 2015).

For the purpose of this study, OA was defined as degeneration of joint surfaces with bone remodelling and spur formation with symptoms of pain, and limited range of motion (Villafane *et al.* 2013; Nicolakis *et al.* 2001). This includes spondylosis, characterised by spur formation, vertebral remodelling and degeneration of ligaments, intervertebral discs, facet joints and

sometimes radiculopathy (Corpurgensli *et al.* 2017; Sokunbi 2015). This correlates with the OA related search terms used for this systemic review, which were spondylosis, degenerative joint disease, degenerative disc disease and osteoarthritis.

2.3.2 Epidemiology of OA

OA affects more than 40 million people in the United States of America. Worldwide it affects roughly 18% of women and 10% of men over the age of 60 years old (Glyn-Jones *et al.* 2015, Taruc-Uy and Lynch 2013). According to Karsdal *et al.* (2016), by 65 years of age, roughly 80% of the population has some radiographic evidence of OA, which concurs with Goode *et al*. (2013) that spinal OA is estimated to range from 40% to 85%. In South Africa, OA was found to have a prevalence of 55.1% in urban settings, while in rural settings, it ranged from 29.5% up to 82.7% among adults over 65 years of age (Usenbo *et al.* 2015).

OA accounts for 2.2% of years lived with disability globally considering all disease, and 10% of years lived with disability when considering only musculoskeletal conditions (Hunter at al. 2014). In terms of years lived with disability, OA is the fastest increasing health condition, with an increase of 64% from 1990 to 2010 (17 million years lived with disability worldwide) (Hunter *et al.* 2014).

Radiographic osteoarthritis has a much higher prevalence than symptomatic arthritis. Also, hand or knee OA had a higher prevalence in women than in men. The risk for knee and hand OA increases rapidly for women between the ages of 50 and 75 years old and the peak is mostly around menopause (Hunter and Bierma-Zeinstra 2019; Prieto-Alhambra *et al.* 2014).

2.3.3 Risk Factors Predisposing a Patient to OA

Different risk factors can lead to, and involves, a combination of mechanical, inflammatory and metabolic factors, with the end result of osteoarthritis, which is failure and destruction of the synovial joint (Hunter and Bierma-Zeinstra 2019; Glyn-Jones *et al.* 2015).

Risk factors for degeneration of these anatomical structures include old age, gender, obesity, bone or cartilage damage due to previous injury, and joint biomechanical deformities or mal-alignments and genetic factors (Silverwood *et al.* 2015; Glyn-Jones *et al.* 2015; Busija *et al.* 2010).

2.3.3.1 Age

Age is the biggest risk factor for OA, due to its exposure to multiple age-related changes that occur in the joint structures (Hunter and Bierma-Zeinstra 2019; Busija *et al.* 2010). These age-related changes may occur because of factors such as muscle weakness, proprioception changes, changes in body weight and a change in gait. Chondrocytes (cartilage cells) also have a decreased ability to repair and maintain tissue as the person ages (Abramson and Attur 2009). This concurs with the discussion in Section 2.2.2, which discussed the normal degenerative process of joints with age.

2.3.3.2 Gender

Being female is another strong risk factor for developing osteoarthritis. According to Busija *et al.* (2010), woman have a 50% higher risk of developing OA than men. Prieto-Alhambra *et al.* (2014) found that the risk of females developing OA of the hand is at its peak around menopause, with more than 3.5 times the risk of developing it between the ages of 50 and 60 years old, compared to men of the same age group. Women who show radiographic signs of knee OA between the ages of 50 and 55 years old had a higher increase risk of death compared to the general population (Busija *et al.* 2010). In addition, a meta-analysis performed by Srikath *et al.* (2005) revealed that females had a significantly higher risk of developing knee and hand OA compared to males. Why females have a higher risk in developing OA is still unknown, but one possible explanation is the oestrogen deficiency following menopause (Busija *et al.* 2010).

2.3.3.3 Obesity

The most common theory described as the cause for OA in obesity is the increase in mechanical forces that are placed on weight bearing joints which may lead to the deterioration of the cartilage (Gly-Jones *et al.* 2015; Berenbaum *et al.* 2013; Abramson and Attur 2009). Many obese individuals also have a varus knee deformity, which increases the forces placed on the medial aspect of the knee, possibly promoting further degeneration (Abramson and Attur 2009). Recent data have shown that obese patients have twice the risk of developing OA of the hand, which is not explained by the joint overload theory which is often used for the knees and hips. Thus, another hypothesis is the role of adipokines, which are cytokines (inflammatory mediators) produced by adipose tissue (fat), that may play a role in OA and obesity (Berenbaum 2013). Obesity has a very strong risk for OA, where 25% of OA cases are found to be due to obesity (Silverwood *et al.* 2015).

A longitudinal study conducted by Mork *et al.* (2012) found that females and males are 4.4 times, and 2.8 times, respectively, more likely to develop OA if they are obese compared to a normal-weight individual. The same study also found that obese and overweight individuals had a very high risk of developing severe OA that limits activity compared to normal weighted individuals. This finding is potentially detrimental for many, as in many countries more than half of their population are either overweight or obese, which can lead to many people being limited in activity (Mork *et al.* 2012).

2.3.3.4 Previous Injury

A previous injury has been found in many studies to be a risk factor that increases the chances of developing OA (Silverwood *et al.* 2015; Muthuri *et al.* 2011; Busija *et al.* 2010; Blegojevic *et al.* 2010; Lohmander *et al.* 2004; Wilder *et al.* 2002). Silverwood *et al.* (2005) found that a previous knee injury was the cause of 5.1% of new cases of OA. In a meta-analysis performed by Blegojevic *et al.* (2010) 14 out of the 16 studies they used found that a previous knee injury was a key cause for developing OA of the knee. It was also found in a study that 42% of female soccer players who have suffered an ACL injury 12 years before had symptomatic radiographic knee OA (Lohmander *et al.* 2004). However, the level of risk varied with many studies mainly because most studies did not provide a detailed explanation of how a previous knee injury was defined (Muthuri *et al.* 2011). A previous knee injury was most commonly established by self-report of the participants. Muthuri et al (2011) showed in their meta-analysis that in most cases, knee injury was not clearly defined, and if it was, the definitions varied. By example one study defined previous knee injury as an injury that was serious enough to hinder weight bearing or required a visit to the doctor because of severe swelling or twisting (Muthuri *et al.* 2011). In contrast, others looked at major knee injuries such as cruciate ligament, meniscal injuries and fractures above or below the knee which would likely increase the risk of OA even more (Muthuri *et al.* 2011). Overall, however, the study found that there was a 4 times higher risk of developing knee OA if the person had suffered a previous knee injury (Muthuri *et al.* 2011). This variance in level of risk can also be seen in a study performed by Wilder *et al.* (2002) where they found that men and women who have suffered a previous knee injury had an increased risk of more than 9 times in developing OA of the knee. Biomechanical deformity / mal-alignment.

Biomechanical factors that are strongly related to the increased risk of developing OA include congenital hip dysplasia (abnormal fitting of femur into pelvis from birth), a CAM deformity, and an unequal leg length (Hunter and Bierma-Zeinstra 2019; Agricola *et al.* 2013; Busija *et al.* 2010) and knee malalignment such as valgus and varus knee alignment showed to have up to

twice the risk in developing OA of the knee (Brouwer *et al.* 2007). Hip dysplasia which is most often caused by a shallow acetabulum is involved in between 20% to 40% of OA of the hip cases (Gala *et al.* 2016). A CAM deformity is cause by the formation of an extra bone at the junction of the head and neck of the femur. This extra bone in certain movements can get forced into the acetabulum which leads to damage to the hip socket and cartilage (Agricola et al 2013). The CAM deformity which is also known as the pistol grip deformity due to the shape it takes, can occur either due to a subclinical slip (slippage of the head on the neck of the femur without symptoms) or more commonly, an abnormality that develops during growth (Tanzer and Noiseuz 2004). Some possible causes of CAM deformities include Legg-Calve-Perthes disease, healed proximal femoral fracture or a bony outgrowth (osteophyte) (Agricola *et al.* 2013).

A study has shown that up to 89% of elite male basketball players who have played their sport from a young age had a CAM deformity versus 8% in nonathletic males. This suggests that CAM deformities can very likely be due to high impact on the joint leading to damage and finally adaptation of the bone (Agricola *et al.* 2013).

2.3.3.5 Daily Activities

There are a wide range of daily activities that have been found to increase the risk of OA which include regular activities such as climbing steps, kneeling and squatting to sports and types of occupations as well. Evidence suggests that standing for longer than 2 hours a day, squatting, bending, kneeling, climbing steps and loading may increase the risk of developing OA (Dulay *et al.* 2015; Blegojevic *et al.* 2010; Busija et al 2010). Sports that were found to increase the risk of OA development included playing soccer, high level long distance running, wrestling and competitive weightlifting. Elite level long distance runners had the lowest risk of 3.3 times the average, while competitive weight lifting increased the risk by 7 times (Driban *et al.* 2017). Those who are less intense with their sporting patterns do not have that increased risk of OA development (Silverwood *et al.* 2015). Finally, some evidence has been found that certain occupations with high levels of physical activity such as farming and construction increase the risk of OA of the knee and hip up to three fold (Hunter and Bierma-Zeinstra 2019; Blegojevic *et al.* 2010; Silverwood *et al.* 2015; Busija *et al.* 2010).

2.3.3.6 Genetic Factors

Genetic factors also seem to play a role in the development of OA with a contribution between 40 % and 80% in hip and hand OA (Hunter and Bierma-Zeinstra 2019; Busija *et al.* 2010). The

strongest factor to the development of generalized nodal OA is genetics, and individual carriers of several defective alleles are more likely to develop OA than a single defective allele carrier (Busija *et al.* 2010). Previously, analysing twins and families has given evidence to show that heritability is also a risk factor for developing OA (Loughlin 2015).

2.3.4 Clinical Features that Allow for the Diagnosis of OA

Diagnosing OA is usually through a clinical evaluation of the patient that presents with deep dull and achy joint pain, short periods of morning stiffness, limited function / restricted movement of the involved joint(s), crepitus, swelling or joint effusion, bony enlargement around the involved joint and joint line tenderness (Taruc-Uy and Lynch 2013). Most often weight bearing joints are involved leading to deep pain worsened by movement (Taruc-Uy and Lynch 2013; Karsdal *et al.* 2016; Hunter and Bierma-Zeinstra 2019).

The diagnostic criteria for OA of the hip as per the American College of Rheumatology (ACR) includes: the presence of hip pain, included reduction of internal rotation of the hip to less than 15 degrees and an erythrosedementation rate (ESR) of less than or equal to 45 mm/hour. Or in the presence of hip pain, if the internal rotation of the hip is more than or equal to 15 degrees, then the internal rotation should be painful, the pain should last less than 60 minutes, and the patient should be over 50 years of age. This classification was found to be 86% sensitive and 75% specific. Both radiographic and clinical criteria combined, hip pain must present with at least two of the following three scenarios: evidence of osteophytes radiographically, evidence of joint space narrowing radiographically and an ESR of less than 20 mm/hour. This criterion was 89% sensitive and 91% specific (Altman *et al.* 1991).

The European League Against Rheumatism (EULAR) criteria for the diagnosis of knee osteoarthritis included both signs and symptoms. Symptoms were, persistent knee pain, knee stiffness lasting less than 30 minutes, and a reduction in physical function. Signs were, crepitus, restricted movement and bony enlargement (Bennell *et al.* 2012). The National Institute for Health and Care Excellence (NICE) criteria for diagnosing knee OA clinically without investigations were as follows: the person was 45 years old or over, the joint pain was caused by activity and the person has no more than 30 minutes of morning joint stiffness (Bennell *et al.* 2012).

No criteria were found on the classification of spinal OA. Thus, in effect, the clinical diagnosis of osteoarthritis is only made when the patient is experiencing symptoms pertaining to osteoarthritis (Glyn-Jones *et al.* 2015). The pain of OA generally comes in two forms, the

continuous background pain or ache, or the irregular but severe pain (Hawker *et al.* 2008). The irregular severe pain has the biggest impact on individuals' quality of life, especially when these irregular bouts are unpredictable (Fu *et al.* 2017). The problem is symptoms only develop when the condition is quite advanced and is potentially irreversible, making it difficult for the early treatment of OA because the treatment is most effective at its early stages (Glyn-Jones *et al.* 2015). When OA is in its early stages, the bouts of pain are predictable and usually occur due to activity. The middle stage is known by constant pain with predictable and unpredictable episodes of pain and movement becomes limited. When OA has reached its advanced stages, the pain becomes more constant, episodes of pain are much more unpredictable, and physical function becomes severely limited (Neogi *et al.* 2010). However, OA sufferers tend to only seek help when they experience symptoms of OA in its middle to advanced stages when damage is quite advanced and effective treatment is difficult or too late (Luyten *et al.* 2018; Glyn-Jones *et al.* 2015). Treatment for OA would be most effective in its early stages, however, there is no consensus on the criteria for identifying early OA (Luyten *et al.* 2018; Glyn-Jones *et al.* 2015).

2.3.5 Special Investigations Used to Diagnose OA

The most common form of investigation for OA is with the use of radiographic imaging. OA in its later stages presents on plain film radiographic imaging with joint space narrowing, osteophyte formation, subchondral sclerosis, osteophytic growths and cysts (Glyn-Jones *et al.* 2015; Taruc-Uy and Lynch 2013; Karsdal *et al.* 2016; Hunter and Bierma-Zeinstra 2019). It is agreed in literature that radiographs should be included in the diagnosis of OA, as this assists in differentiating what stage the disease is in and would also help exclude differential diagnoses, such as stress fractures and osteonecrosis (Luyten *et al.* 2018).

MRI has also been considered as an alternative for detecting changes in OA, as well as detecting early OA (namely, sooner than radiographs) (Guermazi *et al.* 2012). This was shown by a study of 710 participants between the ages of 50 and 90 years old, who showed a Kellgren and Lawrence grade of 0 on radiographs (no signs of OA) where given a MRI. Of those participants, 89% of the knees scanned irrespective of whether they had knee pain or not, had signs of OA which included cartilage damage, osteophytes, bone marrow lesions, synovitis, attrition, subchondral cysts, meniscal lesions, and ligamentous lesions (Guermazi *et al.* 2012). The most common signs of OA seen were osteophytes, cartilage damage, and bone marrow lesions (Guermazi *et al.* 2012). With this in mind, and considering that MRI is also expensive, not commonly available in most primary care facilities and that the structural changes seen in OA tend to be seen in the majority of the population, Luyten *et al.* (2018) suggests that MRI should not be the first choice for investigation.

2.3.6 Impact of the OA

On a patient specific basis, OA mainly involves pain, limited activity, and a large decrease in quality of life (Hunter et al 2014). Direct costs of OA include medication, surgery, clinic visits, in addition to the indirect costs of missed days of work and co-morbidities (Taruc-Uy and Lynch 2013). Seven out of ten OA sufferers experience presenteeism, compared to those who mentioned absenteeism (1/10 sufferers). Those who report absenteeism also have been shown to use more medication (Nakata *et al.* 2018). In one study, absenteeism among OA patients was found to be 2.2 days more than a non OA patient (Menon and Mishra 2018). While in another study, they found that US workers with OA were 1.7 to 2.9 times more likely to miss a day at work coming to about three days of work missed a year on average (Hunter *et al.* 2014).

A much larger issue among the elderly is loss of independence and increased support from others, which comes at a cost to them and their social support network (Taruc-Uy and Lynch 2013; Hunter and Bierma-Zeinstra 2019). This problem is likely to increase as the population ages and the elderly increase in number (Hunter and Bierma-Zeinstra 2019).

Osteoarthritis and diabetes are the causes for the biggest increases in years lived with disability globally (Hunter and Bierma-Zeinstra 2019). By 2020 OA is expected to be the fourth in causes of years lived with disability (Hunter and Bierma-Zeinstra 2019). This is further compounded by a recent meta-analysis that has shown that people with OA are at an increased risk of premature death due to complications associated with cardiovascular disease. This is purported to result from lower levels of activity and an increased inflammatory state which both affect the cardiovascular system negatively (Veronese *et al.* 2016). In addition, OA sufferers also tend to continuously use analgesic medication, which has cardiovascular side effects (Veronese *et al.* 2016). Thus, osteoarthritis sufferers are almost three times more likely to suffer with heart failure or ischaemic heart disease compared with non-osteoarthritis sufferers (Hall *et al.* 2016).

2.3.7 Prognosis of Osteoarthritis

When considering the prognosis of osteoarthritis, having more comorbidities was associated with worse, or a bigger deterioration in outcomes of pain severity and physical functioning (Calders and Ginckel 2018; Nuesch *et al.* 2011). Associated co-morbidities include mainly musculoskeletal conditions (e.g., low back pain, neck pain, hip pain, foot pain, connective

tissue disease and rheumatoid arthritis); cardiovascular conditions and obesity (Suri *et al.* 2010; Nuesch *et al.* 2011; Calders and Ginckel 2018).

Participants from a study who were suffering from at least one musculoskeletal comorbidity where more likely to be suffering from worse symptoms of joint pain from OA (Calders and Ginckel 2018). There was also a significant relationship between a patient suffering with heart disease and/or hypertension and worse results in performance based and self-reported physical functioning which supports previous epidemiological studies (Calders and Ginckel 2018; Nuesch *et al.* 2011). The presence of OA in any finger joint for men was associated with increased cardiac mortality (Busija *et al.* 2010). There is also a tendency to higher rates of death with people that suffer from OA (associated with a walking disability) compared to the general population, particularly with cardiovascular disease (Nuesch *et al.* 2011).

2.3.8 The Treatment and Management of OA

Many therapeutic strategies have been proposed but none have led to both symptom and structural changes to the condition (Glyn-Jones *et al.* 2015). Life style changes including muscle strengthening, range of movement therapy, aerobic conditioning, patella taping, weight loss, social support, bracing, walking aids, shock absorbent insoles, healthy eating habits and education (Stevenson and Roach 2012; Carmona-Teres *et al.* 2015; Hunter and Bierma-Zeinstra 2019) are available to assist patients with OA and are used as first line interventions. Additionally, manual, thermotherapy and electromodality therapies such as manipulation, mobilisation, acupuncture, transcutaneous electrical nerve stimulation, heat and cryotherapy, might be effective for symptom relief (Dwyer et al 2015; Evaniew and Evaniew 2017; Mutlu *et al.* 2018; Hoeksma *et al.* 2004; Poulsen *et al.* 2013; Anwar *et al.* 2018).

2.3.8.1 Dietary and Lifestyle Modification Including Weight Loss and Education

Regarding education, patients must be well informed about OA as well as its pathophysiology, physical changes and impact. Information about the available treatment options which includes regular physical activity, weight loss, specific exercises for the individual, and informing the patient that symptoms can significantly reduce without surgery, are all very important (Hunter and Bierma-Zeinstra 2019).

Obesity and being overweight are known to be major risk factors for the development and progression of OA as they increase the load on joints as well as increase the inflammatory state of the individual (Buttgereit *et al.* 2015). People who have higher BMIs have been found

to suffer with higher pain levels than those with low BMIs even when the severity of OA is considered (Buttgereit *et al.* 2015). Weight loss is also strongly recommended by most guidelines and has been shown to significantly reduce OA symptoms and its progression (Nelson *et al.* 2014). A method used to achieve weight loss with individuals is a change in diet. One study attempted to reduce the weight of 80 participants of whom 71 were woman, with a mean BMI of 35.9 and a mean age of 62.6 years. Half of those participants were placed in a group that received a low energy diet (LED) which was in the form of a nutritional powder as a replacement meal to be dissolved in water. The average loss of weight in the group >10% which resulted in a 28% decline in the clinical presentation of knee OA according to the WOMAC index (Christensen *et al.* 2005).

Another study using a hypo-energetic diet which contained normal food with meal replacements monitored over 16 weeks found that the average weight loss of their participants was 13.7kgs, which lead to a 30% decrease in pain on the visual analog scale (VAS) (Aaboe *et al.* 2011). These compare favourably, when compared to study recording reduction in pain using the WOMAC index in the first year after knee replacement with elderly OA sufferers, they had a reduction of 35% on the WOMAC scale (Bachmeier *et al.* 2001). This also suggests that pre-surgical options of care should be considered prior to surgery that should perhaps be kept as a last resort.

2.3.8.2 Bracing, Strapping/Taping, Walking Aids and Supports

Evidence and agreement in this aspect of treatment is not as widely available as others. However, knee braces, strapping, walking aids and supportive wear were recommended by guidelines for the management of OA in patients (Nelson *et al.* 2014). A study found that there was a statistically significant improvement with the use of valgus bracing for knee OA when compared to a control group without a brace. However, when the control group used a control brace (not meant to have an effect), there was only a small improvement in pain in the experimental group (Moyer *et al.* 2015). This concurs with a meta-analysis that found a valgus brace for knee OA led to a small to moderate reduction in pain (Moyer *et al.* 2015).

Taping of the knee using kinseo tape (KT) was found to significantly reduce pain intensity and maintain it up to four weeks after being treated with KT for one month compared to a control group. It was also reported that the use of KT reduced the patients need to use medication for pain management (Donec and Kubilius 2019). The use of KT was also found to reduce movement triggered pain by 25.7%, which is significant as an improvement of greater than 23% is considered meaningful (Cho *et al.* 2015).

Walking aids (walkers, canes, crutches) were recommended by most guidelines for OA based on whether the individual required it (Nelson *et al.* 2014). It has been shown that walkers, canes and crutches help with improving balance and the overall base of support, which makes the person more stable, therefore preventing falls and further damage (Carbone *et al.* 2013). Wedged insoles have also been recommended to reduce the strain on the knee with medial wedges for lateral knee OA and lateral subtalar strapped insoles for medial knee OA (Hochberg *et al.* 2012).

2.3.8.3 Electrotherapies

Electrotherapies such as Interferential Current (IFC) Therapy and Transcutaneous Electrical Nerve Stimulation (TENS) were both recommended for use in OA patients (Nelson *et al.* 2014). However, the effect gained with IFC and TENS does appear to be very significant. A study was performed to assess the effect of IFC, TENS and short wave diathermy (SWD) compared to sham interventions over three weeks of five sessions per week. All six groups also received supervised exercise and education along with electrotherapies or shams received. At the three month follow up, all groups underwent significant but similar decreases in assessment parameters, except regarding paracetamol consumption which had significantly decreased only in the intervention groups. IFC also maintained the reduced paracetamol consumption at the six month follow up (Atamaz *et al.* 2012).

Vance *et al.* (2012) found in their study that using both low frequency TENS and high frequency TENS increased the pain pressure threshold in participants after their intervention. On the other hand, Palmer *et al.* (2014) found that applying TENS in addition to group education and an exercise programme, compared to group education and exercise programme alone wielded no further benefits or changes in parameters. These inconsistent outcomes in the treatment of OA are either suggestive of the difficulty in being able to attain a homogenous grouping of patients given the complexity of diagnosis and / or the actual inefficiency of the electromodalities as applied in the various clinical contexts due to lack of other predisposing factors that may have induced the OA (e.g., patient weight, genetics, past trauma) that would influence the outcomes of clinical trials due to lack of patient homogeneity.

2.3.8.4 Acupuncture/Dry Needling

Acupuncture involves the insertion of needles into the skin or the thermal stimulation of acupuncture points using low power lasers to relieve pain (de Souza *et al.* 2016; Patil *et al.* 2016). The needles are thin metallic needles that can be manipulated manually or stimulated

electrically (Patil *et al.* 2016). The concept of acupuncture revolves around stimulating the body's energy channels or meridians to restore health by correcting imbalance. One theory is that these acupuncture points are in close proximity to nerves which stimulate the nerves to release endorphins leading to pain relief (Patil *et al.* 2016).

Acupuncture had a mixed response regarding recommendations for its use in OA management. Some guidelines recommended it, others did not, while others strongly recommended against it (Nelson *et al.* 2014). According to one meta-analysis, acupuncture can lead to both short term and long-term benefits in function for patients with knee OA. However, the effects are not sustained in the long term. They also found that acupuncture appeared to have better results than sham acupuncture, usual care or no intervention at all (Lin *et al.* 2016). Other systematic reviews found that most of the trial results were unclear, but positive results were still found for short term improvements where acupuncture reduced pain, improved functional mobility and quality of life. But most of the evidence on this subject was of poor quality which means there is a lack of appropriate evidence (Manyanga *et al.* 2014; Corbett *et al.* 2013). On the other hand, a review of evidence found that of two well designed randomized controlled trials comparing acupuncture to sham acupuncture, little to no evidence was found supporting Mayanja acupuncture to be superior to sham acupuncture (Manheimer *et al.* 2018).

Dry needling is used in the management of pain syndromes by inserting fine needles into tissues such as muscles, ligaments, tendons, fascia, scar tissue and periosteum. It is most commonly used to treat myofascial trigger points (Ughreja and Prem 2021). Ughreja and Prem (2021) found in a systematic review that Dry needling had contradictory results regarding its use on myofascial trigger points in knee osteoarthritis sufferers. But in the case of dry needling by periosteal stimulation, there was moderate evidence in support of its use but only for its short-term effects on pain and function (Ughreja and Prem 2021). An RCT performed by Ceballos-Laita *et al.* (2019) revealed that the short-term effect of dry needling myofascial trigger points around the hip included a decrease in pain intensity, increase in hip ROM and improvement in physical function.

2.3.8.5 Aerobic and Strengthening Exercises

Exercise in the form of both water-based and land-based exercise were strongly recommended by most guidelines (Nelson *et al.* 2014). There is moderate to high quality evidence that exercise improves function and decreases pain significantly when compared to control groups in the short term as well as long term (Fransen *et al.* 2015). The relief in knee OA pain is

equivalent to the improvements found in pain using NSAIDs and analgesics (Fransen *et al.* 2015). The systematic review performed by Fransen *et al.* (2015) revealed that exercises involving quadriceps strengthening yielded the greatest improvements, general lower limb strengthening exercises that may or may not be combined aerobic exercise showed medium effects on improvements in physical function, while walking exercises revealed the smallest benefits. Overall, the quality of evidence in support of exercise was high (Fransen *et al.* 2015). Another systemic review that assessed the possibility of strength training being the superior form of exercise for OA improvement, found that there was no specific exercise protocol that was found to be superior to others regarding improvements in pain and disability. These exercises that were not strength training but also led to similar improvements and included aquatic exercise, aerobic exercise, functional exercise and guided individualized exercise (Bartholdy *et al.* 2017).

Although high quality evidence is present for exercise as treatment for OA (Hunter and Bierma-Zeinstra 2019; Bartholdyy *et al.* 2017; Fransen *et al.* 2015; Fransen *et al.* 2014), its often not the primary intervention utilized in clinical practice and is often poorly implemented (by the practitioner and/or the patient) given their individual and collective environmental circumstances. There may also be fear avoidance behaviour / negative beliefs pertaining to exercise that may need to be overcome by the patient. In the case of weight loss, studies show that combining dietary changes with exercise yield better results than just either one by themselves (Hunter and Bierma-Zeinstra 2019).

2.3.8.6 Non-invasive Manual Therapy: Range of Motion Therapy/Manipulation and Mobilisation

Manual therapy involves treatment using the hands to manipulate, adjust, mobilise, massage or create traction in the body (Bergmann and Petersen 2011). Manipulation and mobilisation behave been found to be effective for symptom relief (Dwyer et al 2015; Evaniew and Evaniew 2017; Mutlu *et al.* 2018; Hoeksma *et al.* 2004; Poulsen *et al.* 2013; Anwar *et al.* 2018).

Several studies have found that specifically manual therapy with or without exercise or patient education may be beneficial in reducing pain, as well as increasing physical performance, range of motion and function (Anwar *et al.* 2018; Hoeksma *et al.* 2004; Poulsen *et al.* 2013), without the attendant side effects of medication or surgery. Altinbilek *et al.* (2018) found that osteopathic manual therapy together with exercise in the form of muscle strengthening and aerobic exercises reduced pain and improved physical function more than exercise by itself. Another study found that manual therapy led to a greater decrease in the WOMAC score with

33.1 points over usual care versus exercise therapy with 14.3 points over usual care (Abbott *et al.* 2013). The combination of both manual therapy and exercise did not lead to a significant additional benefit (20.9 points over usual care) (Abbott *et al.* 2013). Hoeksma *et al.* (2004) also found that pain, hip function and general improvement were significantly better with participants who received manual therapy compared to exercise. The primary outcome measure in the study was using a six point Likert scale which ranged from much worse recovery to complete recovery, which revealed manual therapy having an 81% success rate compared to exercise at 50%. This meant that 81% of participants reported “improved”, “much improved” or “complete recovery” on the Likert scale following the intervention (Hoeksma *et al.* 2004).

Manipulation and mobilisation are both physical movements performed to cause joint motion through either thrust techniques (manipulation) or non-thrust techniques (mobilisation) (Bergmann and Petersen 2011). Studies have shown the benefit that manual therapy can play in treating osteoarthritis but due to the limited amount of high quality research on OA, it is not recommended enough as a form of treatment for OA Currently, weight loss and exercise are the most recommended for OA (Nelson et al 2014). However, with the benefits of manual therapy that is either equivalent or greater than exercise, it should be recommended at a similar level.

Manipulative therapy: A form of manual therapy, which involves high velocity, low amplitude thrusts applied to a joint (Hengeveld and Banks 2005). Manipulation is derived from the Latin word *manipulare*, meaning the use of the hands in a skilled manner or skilled treatment by hand. Therefore, manipulation can mean soft tissue manipulation, massage, manual traction and joint manipulation (Hengeveld and Banks 2005). In the case of this study, manipulation refers to joint manipulation. Manipulation is also defined as a grade 5 mobilisation where the technique is performed at such a speed that does not allow the patient to prevent it. This gives it the description of a high velocity (very quick), low amplitude (low force) thrust performed at the end of available range (Hengeveld and Banks 2005).

Joint segments are selected based on palpatory hypomobility and stress tests (Bergmann and Peterson 2011). This diagnosis of joint dysfunction syndrome identifies locally altered joint mechanics. One of the commonly proposed sources of joint fixation or hypomobility is tissue injury resulting in fibrosis (adhesion formation), loss of elasticity (increased collagen stiffness) and loss in strength (due to arthrogenic muscle inhibition). The injury can be due to acute or repetitive trauma which leads to an inflammatory response which through a chain of events that eventually leads to decreased joint motion (Bergmann and Peterson 2011). Immobilisation

slows the recovery process, decreases natural nutrition to the joint (decreased synovium) and increases the rate of degeneration, eventually leading to loss of soft tissue flexibility and muscle strength and possible inter-articular fatty adhesions. Thus, manipulation aims to restore motion, to improve and facilitate recovery.

Manipulative procedures are manoeuvres that induce joint motion through thrust techniques or manipulation (Bergmann and Petersen 2011; Cao *et al.* 2013). The thrust is delivered at the restrictive joint barrier or the direction of reduced joint motion to increase range and quality of motion as well as decrease pain (Boff *et al.* 2020; Bergmann and Petersen 2011).

Several studies have found that specifically manual therapy with or without exercise or patient education may be beneficial in reducing pain, increasing physical performance, range of motion and function (Anwar *et al.* 2018; Hoeksma *et al.* 2004; Poulsen *et al.* 2013; Dwyer *et al.* 2015), without the attendant side effects of medication or surgery.

Mobilisation therapy is a form of manual therapy with multiple techniques, such as, mobilisation with movement and Maitland accessory glides (Maitland 1991). It is passive or active movements performed in a manner and speed that are within the control of the patient and if the patient chooses so, they can prevent it (Hengeveld and Banks 2005). This can be in the form of a stretching technique performed at or near the end of range of motion aiming to elongate connective tissue (Blackman and Atkins 2014; Hengeveld and Banks 2005). It can also be performed as passive oscillatory movement with varying applied within the range of movement and can be repeated for up to a few minutes depending on joint or soft tissue effects desired (Hengeveld and Banks 2005). These mobilisation movements can also contain accessory movements that a person cannot perform by themselves, and are performed by the practitioner. The desired effect of mobilisation, in the case of a meniscus tear (which leads to limited joint range of motion), is to use these passive joint movements to increase range of motion and become pain free (Hengeveld and Banks 2005).

Grading of mobilisation is used to indicate the extent of the position chosen in the available range of motion and are from grade 1-5. Grade 1 is a small amplitude movement performed at the beginning of available range, Grade 2 is a large amplitude movement performed within the resistance free part of available range, Grade 3 is a large amplitude movement performed up to the limit or resistance of available range, Grade 4 is a small amplitude movement performed into the end range or resistance of available range and Grade 5 is a high velocity, low amplitude movement performed at the end of available range but may not always be at the end of

available range. Mobilisation lies within grade 1-4 (Hengeveld and Banks 2005), with manipulation considered a Grade 5.

In a study performed by Bhanushali *et al.* (2017), they were able to show that in people suffering with lumbar spondylosis, lumbar facet mobilisation in addition to Transcutaneus Electrical Nerve Stimulation (TENS) and Mechanical Intermittent Lumbar Traction (MILT) lead to significant improvements compared to only TENS therapy and MILT in the control group. Although improvement was found in the control group (7.74 to 6.4 on the visual analog scale (VAS)), the experimental group showed greater improvement (7.61 to 2.47 on the VAS). Significant increase in lumbar mobility was also found compared to the control (Bhanushali *et al.* 2017). Copugensli *et al.* (2017), found that Mulligan's mobilisation in addition to conventional rehabilitation led to better outcomes in range of motion of neck in extension, left rotation and right rotation compared to the control group that only received conventional rehabilitation. A case report performed by Crowell and Tragord (2015) found that mobilisation and exercise for a patient with glenohumeral joint OA performed over eight weeks reduced shoulder pain and disability index score from 43% to 4% with functionality also increasing significantly. A booster session was performed at nine months for four sessions which assisted in maintaining the outcomes for one year.

Considering the effects of manipulation and mobilisation, the treatment of OA with manipulation or mobilisation has not been studied adequately and, thus, needs to be a topic of study to further understand manipulations place in the treatment of OA. Thus, the purpose of this study was to collect all available studies on the treatment of OA of the spine, hand, shoulder and TMJ. Then rate the studies based on their quality and identify further gaps in research that needs to be explored,

2.3.8.7 Pharmacological Management

Pharmacological interventions (such as oral paracetamol and NSAIDs) are generally used for symptom control (Glyn-Jones *et al.* 2015; Hunter and Bierma-Zeinstra 2019).

Topical NSAIDs were found to be effective compared to placebo for pain relief in a 2018 study (Zeng at al. 2018). If a patient has not responded to oral or topical NSIADS, intraarticular corticosteroids are advised however a review in 2015 revealed the effect of intraarticular corticosteroids is unclear due to low quality trials (Juni *et al.* 2015). One study found that the injection of intra articular steroids every three months over two years resulted in a significantly greater amount of cartilage loss with no significant change in knee pain compared to a group

that received saline injections (McAlindon *et al.* 2017). Which indicates the risk involved with corticosteroid injections and the likely progression of OA.

Another new treatment option is duloxetine which is a serotonin and norepinephrine reuptake inhibitor, compared to a placebo, was found to reduce pain and improve function with acceptable side effects (Wang *et al.* 2015; Uchio *et al.* 2019). Opiates on the other hand were found to be of small benefit compared to their side effects as well as having a risk of addiction (Ackerman *et al.* 2018). Disease modifying drugs for OA are under investigation but the majority have limited success or failure due to increasing side effects or no change in the patient's clinical picture (Karsdal *et al.* 2016; Glyn-Jones *et al.* 2015). This means that at the very best disease modifying drugs provide a "hit-and-miss" treatment where some patients benefit, others have significant side effects and yet others have no effect at all (Karsdal *et al.* 2016).

As shown above, medication have their place with symptom management in OA. However, at their current stage they are not the answer to solving the progressing problem of OA and the side effects associated with medication also needs to be kept in mind (Hunter and Bierma-Zeinstra 2019; Karsdal *et al.* 2016; Ackerman *et al.* 2018; Glyn-Jones *et al.* 2015).

2.3.8.8 Surgical Management

By comparison surgical approaches are used to relieve pain, correct structure or when conservative treatment approaches have failed.

Joint replacement surgery, which is the most common treatment in knee OA, is considered cost effective if only used for end-stage OA patients where the patient suffers with joint pain that disturbs their regular sleep patterns, severely reduces their walking distance, significantly restricts their acts of daily living, where all conservative approaches applied for six months have failed and their quality of life is greatly reduced (Hunter and Bierma-Zeinstra 2019; Culliford *et al.* 2012). But this should be seen in the context that up to 20% of total knee replacement (TKR) patients post-surgery gained little benefit or found a poor outcome (Price *et al.* 2018). Wylde *et al.* (2010) found that 44% of TKR and 27% of total hip replacement (THR) patients complained of post-surgical pain. Although most were mild in severity, 15% of TKR and 6% of THR patients reported severe-extreme post-surgical pain. Complications include venous thromboembolism, infection, neurovascular injury, prosthetic joint infection and wear and tear of prosthesis.

Furthermore, arthroscopic knee surgery**,** which is widely used for knee OA lacks evidence, and has shown to have minimal benefit and an obvious risk of harm (Hunter and Bierma-Zeinstra 2019; Richmond *et al.* 2009). Patients with knee OA who undergo arthroscopic knee surgery with meniscectomy are three times more likely to have knee replacement surgery (Rongen *et al.* 2017). Similarly, for lumbar spinal stenosis (secondary to degeneration), the rate of side effect occurrence due to surgery ranged from 10% to 24%. Complications included lesions to the dural sac, neural dysfunction due to peridural haematoma, spinous process fracture and pulmonary oedema (Zaina *et al.* 2016).

From the preceding literature, it can be seen that there are various interventions that may be applied to a patient with OA (to a specific joint) or group of joints. The surgical interventions seem to be applied in cases where conservative therapy or pharmaceutical interventions have not provided relief for the patient. It is however also clear that there seems to be very little evidence in the treatment of OA outside of the knee and hip, where the majority of the literature seems to be focused. Given the increasing pandemic of obesity and the growth of the aging population, it is becoming an increasing necessity to explore the other intervention options to better manage OA (particularly in other body regions) in order to allow practitioners to be able to apply evidence based practice principles in their every day practice. The process is usually preceded by a review of the available literature in order to determine what exists with the aim to make recommendations on future studies that may be beneficial. Therefore, the next section provides a short overview of what a systematic review is.

2.4 SYSTEMATIC REVIEWS

2.4.1 Outline of a Systematic Review

Systematic reviews are known for their methodological rigor and are thus the reference standard for incorporating evidence in health care (Moher *et al.* 2015). Systematic reviews can be performed on all types of research, which include randomised trials, cross-sectional studies, cohort studies and qualitative research (Clarke 2011). A systematic review attempts to collect all relevant studies in an attempt to answer a specific research question where in the case of this systematic review, the question was related to what evidence exists in terms of the effectiveness of manipulation and mobilisation in the treatment of OA. The evidence collected based on a pre-specified eligibility criteria (in this study, eligibility was based on key terms present in the title, which are “manual therapy”, “manipulation”, “mobilization”, “osteoarthritis”, “spondylosis”, “degenerative joint disease” and “degenerative disc disease”) used a systematic

method to minimize bias where conclusions and decisions can be made from (Liberati *et al.* 2009; Clarke 2011).

The characteristics of a systematic review are, a clear set of objectives with a reproducible methodology, a systematic search that identifies all studies that meet the eligibility criteria, assessing the validity of each study, and lastly a presentation and incorporation of the findings from the included studies (Moher *et al.* 2015; Ahn and Kang 2018). The evidence is then synthesised which may or may not include a meta-analysis dependent on study type inclusion (Clarke 2011) which in the case of this systematic review, a meta-analysis was not included due to the variation in study types. A detailed outline and explanation of how this systematic review was performed will be explained in Chapter Three.

2.4.2 The Role of a Systematic Review

The main purpose of a systematic review is to evaluate the evidence that articles within a particular domain present for or against a particular intervention or set of interventions (Ahn and Kang 2018). This information is then used in the development of clinical practice guidelines and clinical practice decision making (Moher at al. 2015).

The review of the available evidence is made on the basis of an analysis of the published articles and how they contribute to building a body of evidence. In this respect for an article / study to be of good quality it needs to be **internally and externally valid**. Internal validity involves minimizing bias in clinical trials which is compromised by anything surrounding the method of how the trial is performed leading to a difference in the true values that should be attained. They fall within 4 categories: selection bias, performance bias, detection bias and attrition bias. External validity is how generalizable the results of the trial are back to the population and different circumstances. This is dependent on the population, the setting, the treatment regimens and the measurement variables used in the trail as well as the in its clinical use (Juni *et al.* 2001).

Firstly, it is important for the authors to have set a specific **inclusion and exclusion criteria** for the population that they are targeting and that are the most appropriate for their research. That target population must also be realistic, accessible to them, and be representative of the general population to not compromise the external validity of the study. The exclusion criteria of the study will be what characteristic of the patient will be excluded due to possible contraindications to the intervention such as osteoporosis in a manipulation intervention, or the

patient presenting bias into the study, such as having received the same intervention recently (Kendall 2003).

Once participants have been found, they need to be randomly assigned to the experimental or control group in a way where the control group is similar to the experimental group to prevent the occurrence of **selection bias** (Akobeng 2008). The **randomization** should also distribute them in a way to prevent confounding variable from causing bias in the results (Akobeng 2008; Kendall 2003). When participants are being randomised, each one should have an equal chance of being assigned to either one of the intervention groups which can be performed using a computer algorithm, tossing a coin, or throwing a dice (Keirse and Hanssens 2000; Juni *et al.* 2001 Akobeng 2008).

An important part of conducting unbiased research is having **patients that are naïve to the intervention** of choice. A participant having preconceived perceptions about one treatment method compared to another can lead to bias in the results. This can occur by the participant either assuming because it is a new and expensive treatment, they may report to be better than they really are, or if they have received the treatment previously, they may already be biased to one treatment over the other (Akobeng 2008; Moustgaard *et al.* 2014). It has been found that not blinding versus blinding participants in a trial can lead to an exaggeration of the effect size of an intervention (Moustgaard *et al.* 2014).

Wash out periods are mainly used in drug interventions to prevent a previous drug that was used from causing false results. When it comes to slow acting symptom modifying drugs, between 3–6 months of a wash out period should generally be considered especially in cases where the drug being used in the intervention is a slow acting drug for symptom relief (Maheu *et al.* 2006). A longer washout period such as 12 months can help ensure internal validity, but this can exclude participants who are suffering with more severe symptoms or those who are in the later stages of their condition (Roberts *et al.* 2015; Johnson *et al.* 2013). So, although the estimates would be less bias using a group who have had a long wash out period, these results may not apply to many patients with the condition (Roberts *et al.* 2015; Johnson *et al.* 2013). Ideally, having a wash out period that only excludes that specific intervention such as not having any form of manipulation for 3-6 months for a manipulation intervention but allowing all other forms of complimentary therapy, may be appropriate (although these would need to be considered on a patient by patient basis).

Uncontrolled medication use is another major factor that can influence the results leading to bias and false positives. Medication can reduce joint pain and muscle aches that the participant

may be experiencing especially if the patient changed their prescription or changed the dosage that they may be taking (Valdes *et al.* 2017). In many cases, participants need to medicate due to the severity of their condition, but this can be managed by stopping intake of analgesics, muscle relaxants or anti-inflammatory drugs a few days before examination and outcome measures are taken at baseline and at following measurements (Villafane *et al.* 2013).

For **selection bias** to be prevented, blinding of participants needs to have occurred at an adequate level. Blinding occurs when everyone (participants, investigators, outcome assessors) or at least 1 or 2 of the groups are unaware of which intervention is assigned to what group (Renjith 2017). A single blinded study involves blinding of anyone group (participants, investigators, assessors), usually it is the participants receiving the intervention or the outcome assessors that are blinded in this case. A double blinded study is one any two groups are blinded, usually it is the participants and the outcome assessors. While a triple blinded study is when all groups are blinded which will introduce the least amount of bias into the study (Renjith 2017). However, double blinding is not always possible or appropriate in a study such as studies where the participants receive interventions involving surgery, rehabilitation, exercise, dietary, psychological or educational modifications. However, one group that can be blinded to limit bias in the study are the outcome assessors (Akobeng 2008; Renjith 2017). When blinding of outcome assessors does not occur responses by the outcome assessors tend to be exaggerated compared to studies where blinding has occurred (Moustgaard *et al.* 2014; Renjith 2017).

Selection bias can also be affected when a study lacks allocation concealment. Allocation concealment is the process by which investigators, outcome assessors and participants and prevented from knowing to which group a participant will be assigned to before they enter the study (Viera 2007; Akobeng 2008). If allocation concealment is not performed or is inadequate, investigators, outcome assessors and participants can influence to what group the participants are assigned to which negates the effect of randomization (Viera 2007). In studies where there was a lack of allocation concealment, there was an exaggeration of up to 41% of results compared a study where allocation concealment occurred (Akobeng 2008).

Performance bias refers to a difference in the care that is given between groups where one groups is given preferential treatment over the intervention group or vice versa (Moustgaard *et al.* 2014; Akobeng 2008; Renjith 2017; Juni *et al.* 2001). This form of bias can occur because the investigator may be in favour of the intervention giving extra attention to the patient compared to what the control group receives, or emphasizes on the benefits of the intervention to the participant more than the emphasis that is given to the control group. Another source of

performance bias is having only one therapist applying the intervention to both groups which can also lead to a difference in interaction dynamics due to the therapist knowing which group is experimental and which is the control (Kendall 2003; Renjith 2017).

Detection bias occurs when the outcome assessor has knowledge of the participant's group assignment leading to undue favour in the assessment or exaggeration of the results or the intervention group (Juni *et al.* 2001; Akobeng 2008). The outcome assessor may over analyse one group's data over the other for small differences that may help support one intervention over the other. These biases can be eliminated with the use of blinding and allocation concealment.

Attrition bias is defined as a systematic difference between the two groups being compared due to participant loss from the study (Juni *et al.* 2001; Akobeng 2008). This occurs after a participant has already been allocated to a group and is lost by either exclusion, such as deviation from protocol, or a clinical decision to stop the intervention due to unforeseen circumstances, or the participant drops out of the study by becoming uncontactable or refuses to participate any further (Juni *et al.* 2001). To prevent these unforeseen circumstances from causing bias in a study, all participants that are randomised into groups should be included in the analysis and remain in their groups whether or not they received the treatment intervention or were available until the completion of the study. This method of analysis is known as the intention to treat principle (Akobeng *et al.* 2008; Juni 2001). Although this analysis does not require the patient to continue in the study, the mathematical calculations do potentially still have the capacity to over or under value the improvements / regression by the patient as the calculations are performed on the initial improvements that the patient made whilst in the trial. Another factor that can lead to bias in results is chance or random error. This tends to occur because of a small sample size, whereas studies with a large enough sample size can minimize the occurrence of random error considerably (Kendal 2003; Akobeng 2008). Small sample sizes have higher risks of false negatives and positives, where either the effect size is much smaller than what it should be or much larger than what it should be due to chance (Keirse and Hanssens 2000).

Finally, external validity is the ability or extent that results can be generalised back to the population (to the real world) and to other clinical settings and circumstances without being in trial settings. An issue arises with RCTs where they are not reported in a way that allows practitioners to decide who the results can be applied to (Akobeng 2008; Rothwell 2005). The external validity in many RCTs are limited in the aspect where a treatment method can be strongly influenced by the doctor patient relationship and placebo effects which can leave

results severely underestimated in an RCT (Jones *et al.* 2009; Rothwell 2005). Trials eliminate this aspect with the addition of blinding, placebo control, allocation concealment and the exclusion of clinicians and participants who have a strong preference to a certain type of treatment (Rothwell 2005). Other factors that can compromise the external validity of a study include participants being chosen from secondary or tertiary care rather than primary care facilities, participants with multiple or progressed co-morbidities are excluded, protocols in trials can differ from clinical practice such as before starting the trail, a patient needs to see a neurologist as well as receive a certain scan which is not the norm in clinical practice. Inadequate duration of treatment and follow up can also limit the external validity of a study (Rothwell 2005; Jones *et al.* 2009).

It is important to choose outcomes that will identify the most important changes from an intervention (Coster 2013). Such as in the case of mobilisation, those would include, pain, range of motion, muscle activity and strength, so outcome measures that would directly measure those outcomes would be the most beneficial and the most likely to give outcomes (Coster 2013).

It is also important that the researcher knows that the outcome measure chosen is will respond in time between the intervention and the measurement of the outcome. Therefore, the researcher needs to measure the outcomes at point that make sense and provide knowledge of the condition (Coster 2013).

2.4.3 Systematic Review of Randomized Clinical Trials

Concerning the internal review of RCTs, the PEDro scale is found to be the scale of choice. The reliability of rating of PEDro scale items varied from “fair” to “substantial”. Whereas, the reliability of the total PEDro score was “fair” to “good” (Maher 2003). Through consensus judgments for the reliability of the PEDro scale, it was taken as acceptable and to be reliable enough for its use in systematic reviews of RCTs pertaining to physical therapy (Maher 2003).

2.4.4 Systematic Review of Non-Randomized Controlled Trials

The appraisal of non-randomized controlled trials is most commonly performed using the Newcastle Ottawa scale and has been endorsed by the Cochrane collaboration (Wells 2003; Hartling 2013; Quigley 2019). The overall reliability score for the NOS scale was “fair”. However, the inter-rater reliability was found to be poor, and the scale needed more evidence to support its use in systematic reviews (Hartling 2013). There is also no evidence that the

NOS is able to identify studies with biased results (Hartling 2013). Deeks *et al.* (2003) found that their reviewers found the scale easy to use and was agreed on to be suitable for systematic review use. Li *et al.* (2008) also reported that the NOS was reliable and valid for use. However, Stang (2008) said that the NOS contains items that are problematic as well as uncertain validity. Agreement on the scale varied and he also said that there is no evidence that has shown that NOS can identify trials with biased outcomes.

Overall, responses vary with how effective the NOS is in detecting bias in nRCTs, but since it is the most popular and is found to be acceptable by some studies, it was chosen as the scale for nRCTs. In this review, the appraisal of all non-randomized trails was performed using the Newcastle Ottawa scale.

2.4.5 Systematic Review of Case Reports and Case Series

The JBI critical appraisal tool for case series was found to be reliable and applicable for the appraisal of case series, while the JBI critical appraisal tool for case reports was found to be reliable and applicable for the appraisal of case reports.

2.5 CONCLUSION

Chapter Two described OA through its definition, its proposed pathogenesis, its risk factors and its most common methods of treatment. Manipulation and mobilisation were also highlighted in this chapter to show the impact that is can also have on OA treatment and management. Gaps in knowledge were then discussed as well as the role a systematic review will play in addressing those gaps. Following this, Chapter Three outlines the methodology used in the process of this systematic review, which includes the development, appraisal and analysis of the studies that fall within this systematic review criteria which will allow conclusions to be drawn on the results and recommendation to be made.

CHAPTER THREE RESEARCH METHODOLOGY

3.1 INTRODUCTION

This chapter describes the methodology of this study, the research design and approval, the study procedure, the preliminary search, the study selection and finally the quality assessment.

3.2 RESEARCH DESIGN AND APPROVAL

The study design was a quantitative-qualitative (the quantitative data is gained from the reviews and reviewers while the qualitative portion involves the contextual analysis for bias) paradigm study using a systematic review approach (Higgins and Green, 2011). This study design required that all relevant articles pertaining to the use of mobilisation and manipulation in the treatment of OA, be systematically and methodologically screened; methodologically obtained via electronic databases and critically evaluated for their methodological rigor. Therefore, this review protocol was structured according to PRISMA guidelines (Appendix O) (Moher *et al*. 2009).

The study was approved by the Faculty Research Committee at the Durban University of Technology (Appendix L). There was also partial funding by the Durban University of Technology. An agreement from the reviewers selected was made using a Memorandum of Agreement (MoA) (Appendix C). Copyright permission for the distribution of articles was obtained before assigning to reviewers (Appendix M). The study was also be registered with PROSPERO (Appendix N).

3.3 STUDY PROCEDURE

A literature review was conducted on multiple databases/search engines (DUT Summons, Pubmed, Scopus, CINAHL and Google Scholar) using the relevant key search terms that aligned with the established inclusion and exclusion criteria outlined below.

3.3.1 Inclusion Criteria

a) All relevant citations were required to be available in electronic format.
b) Citations needed to have the following relevant keywords in the title: One of the following keywords **“manipulation”**; **“mobilization”**; **“manual therapy”** and one of

the following keywords **“osteoarthritis”**; **“spondylosis”**; **“degenerative joint disease”**; **“degenerative disc disease”** (Appendix A).

3.3.2 Exclusion Criteria

a) Non-English articles (Crowther *et al.* 2010).
b) Titles involving the treatment of non-human participants (Seok *et al.* 2013)
c) Articles defined as systematic reviews, narrative reviews, and summaries (Crowther *et al.* 2010).
d) Book chapters (Crowther *et al.* 2010).

3.3.3 Inclusion of Articles Through Abstracts

1. The title needed to comply with the inclusion and exclusion criteria mentioned in step 1.
2. The abstract needed to have one of the following terms “**manual therapy**”; “**mobilization**”; “**manipulation**” as one of the treatment modalities being used in human adult subjects.
3. The abstract needed to state that one of the following terms “**osteoarthritis**”; “**spondylosis**”; “**degenerative joint disease**”; “**degenerative disc disease**” as the condition being treated by the treatment modalities mentioned above.
4. Studies were required to be in English or translated to English (Crowther *et al.* 2010).
5. The types of studies included were randomised controlled trials, non-randomised controlled trials, case studies, and case reports.

3.3.4 Exclusion of Articles Through Abstracts

1. Non-English abstracts or articles (Crowther *et al.* 2010).
2. Abstracts involving the treatment of non-human participants (Seok *et al.* 2013).
3. Abstracts that do not involve treatment by either manipulation or mobilisation.
4. Abstracts involving the treatment of the knees or the hips.
5. Studies that were protocols or guidelines for studies to be performed (Crowther *et al.* 2010).
6. Studies that were systematic reviews / summaries / narrative reviews (Crowther *et al.* 2010).
7. Articles that were conference papers, posters, or workshops (Crowther *et al.* 2010).
8. Duplicate studies found during the review process (Crowther *et al.* 2010).

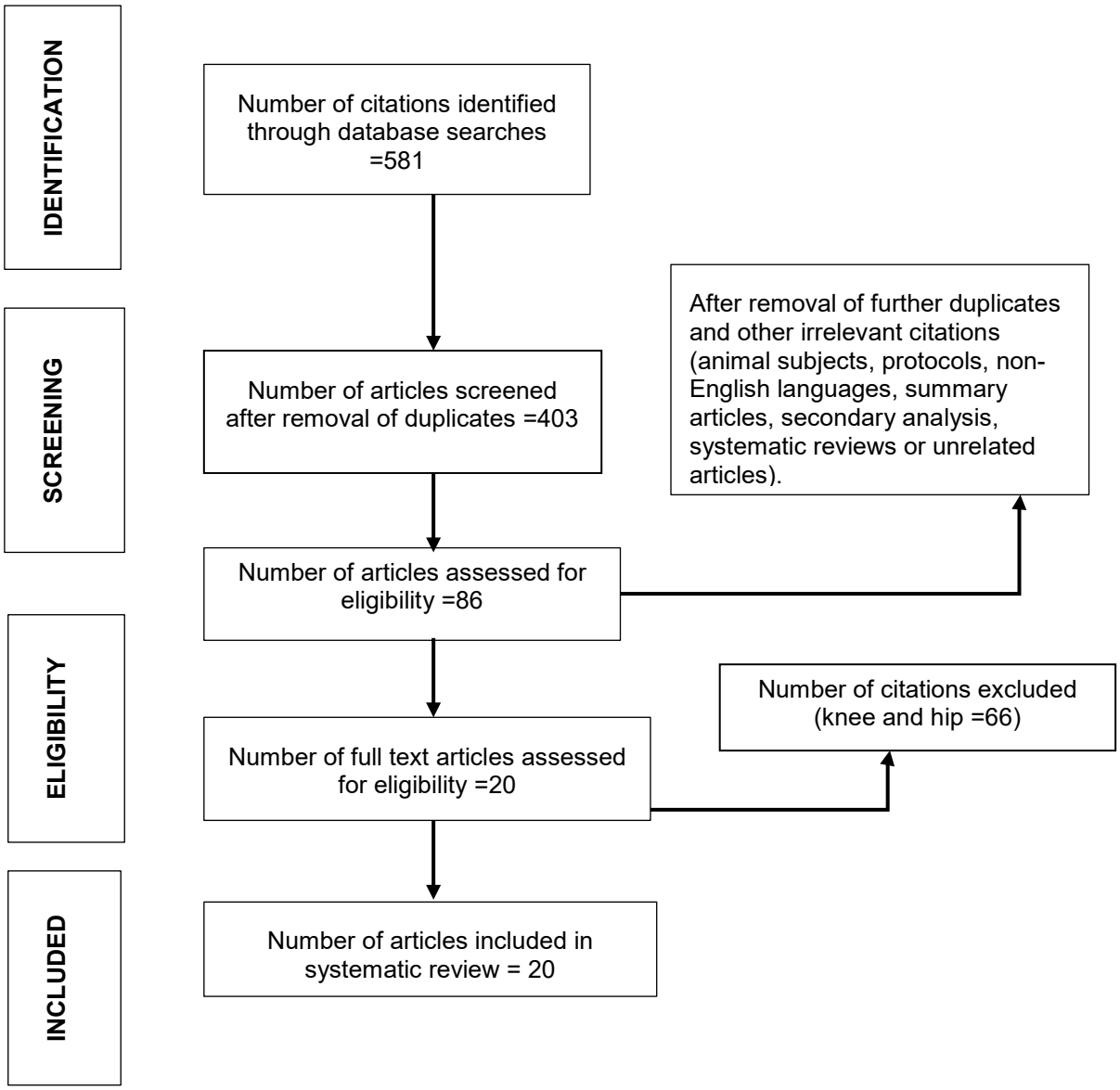

Figure 3.1 Flow diagram illustrating the search strategy based on the PRISMA statement

3.4 PRELIMINARY SEARCH

3.4.1 Database Search

The databases where comprehensive searches were performed to identify any articles related to the topic of manipulation and mobilisation for OA included:

- CINAHL.
- Google scholar.
- PubMed.
- Scopus.
- DUT Summons.

According to the postgraduate librarian (Ms Avenal Finlayson) at DUT, DUT summons includes articles from multiple databases which include:

- Ebscohost (which includes CINAHL, MEDLINE and others).
- Gale Academic.
- Springer Nature Journals.
- Cochrane database of systematic reviews.
- ClincalTrials.gov.
- ScienceDirect.
- SAGE Knowledge.
- Directory of Open Access Journals.
- JSTOR.
- BASE.
- Emerald Insight.
- SpringerLink.
- Proquest.
- Web of science.

3.4.2 Search Terms

An article needed to have two key words in its title to be included in the search:

1. One of the following key words “manipulation”, “mobilization” or “manual therapy”.
2. One of the following key words “osteoarthritis”, “spondylosis”, “degenerative joint disease” or “degenerative disc disease”.

Table 3.1 Number of citations per search engine

Search engine	Summons	Google scholar	PubMed	CINAHL	Scopus
Citation number	52	160	45	41	105

There were many articles from these databases that were duplicates with more than one database containing the same article that met the inclusion and exclusion criteria. These articles were then later removed as per the study selection criteria.

3.5 STUDY SELECTION

3.5.1 Screening of Articles

The citations generated from the chosen databases were saved in a citation library (EndNote) and further analysed to identify those that still fell within the inclusion and exclusion criteria based on their abstracts and finally their full texts shown in Table 3.2. The criteria for inclusion and exclusion of articles based on their abstracts and full tests were mentioned in Section 3.3.2, 3.3.3 and 3.3.4.

Table 3.2 Number of articles included per search engine

Search engine	Summons	Google scholar	PubMed	CINAHL	Scopus
Number of articles	2	2	3	2	11

3.5.2 Secondary Search

A secondary search was conducted known as the hand search to identify any further relevant articles that complied with the inclusion and exclusion criteria (Vassar *et al.* 2016). Through this secondary method, there were no further articles that were identified by the researcher.

3.5.3 Final Allocation

These articles were then sorted into a masters list of articles (Appendix B) which included all the articles that fell within the inclusion and exclusion criteria for citations and abstracts. The full text articles were then sourced, and further reviewed to identify what type of category of research they belonged to. The studies were then categorised as randomised controlled trials, non-randomised controlled trials or observational studies using this method:

1. Full texts that describe the random allocation of participants were categorized as randomised controlled trails.
2. Full text that did not describe the randomisation of participants but involved grouping of participants for comparison were categorised as non-randomized controlled trials.
3. Full text that described the observation of a patient or patients care without the use of grouping for comparative reasons were categorised as observational.

Table 3.3 Number of articles per study type

Study type	RCTs	nRCTs	Observational studies
Number of articles	11	3	6

3.6 QUALITY ASSESSMENT

3.6.1 Study Types and Measurement Tools

All included studies were assessed using a relevant scale to the study type:

a) RCTs - The scale chosen for this study type was the PEDro scale (PEDro scale 1999) (appendix D) due to its relevance in the appraisal of physical therapy trials. The scale is widely accepted and is sufficiently reliable to be used for the review of physical therapy RCTs in systematic reviews (Maher *et al.* 2003). When using the score to decide between high and low quality RCTs, it must be known total score measurement standard of error is 0.70. This means that when two studies are compared and have a PEDro score difference of 1, there is a 68% that the studies actually had different PEDro scores. A PEDro score difference of 2 mean that there is a 96% confidence that the studies were truly different in PEDro scores (Maher *et al.* 2003).

   The PEDro scale only measure one aspect of a trial which is the methodological quality (internal validity) of study, but assesses it at a reasonable breadth. In addition, none of the 10 items of the scale were found to be unnecessary so it can confidently be used by reviewers so assess the quality of physical therapy trials (de Morton *et al.* 2009). When the scale is being completed, a total of 11 criteria can be answered with a yes or a no with every yes counting as 1 point coming to a total of 11 points for a trial where all criteria have been fully satisfied (de Morton 2009; Maher *et al.* 2003; PeDro scale 1999). The 11 items are, specified eligibility criteria, random allocation, allocation concealment, similarity at baseline, subject blinding, therapist blinding, assessor blinding, more than 85% follow up for at least 1 key outcome, intention to treat analysis, between group statistical comparison for at least 1 key outcome and point measures and measures of variability for at least one key outcome (PeDro scale 1999).

b) n-RCTs – The scale chosen for n-RCTs was the Newcastle-Ottawa scale (NOS) (Appendix F) due it having a fair overall reliability which can cover both cohort and case control studies (Hartling *et al.* 2013). Deeks *et al.* (2003) found that their reviewers found the scale easy to use and was agreed on to be suitable for systematic review

use. Li *et al.* (2008) also reported that the NOS was reliable and valid for use. On the other hand, Stang (2008) said that the NOS contains problematic items with a validity that is uncertain. Agreement on the scale varied and there is no evidence that has shown that NOS can identify trials with biased outcomes. The reviewers also found the scale difficult to use and even with additional information provided to them on answering items and deciding on its level of bias, the items and their responses were still considered vague (Hartling *et al.* 2013; Stang 2008). The responses vary with the regards to the effectiveness of the NOS for detecting bias in n-RCTs, however, currently, there has not been a scale for n-RCTs that has been identified as reliable and valid. Which brings us to the NOS which is widely used and found to be an acceptable scale for

n-RCTs (Wells *et al.* 2003; Hartling *et al.* 2013; Deeks *et al.* 2003; Li *et al.* 2008).
The NOS assesses the quality of a n-RCT from the following aspects: selection of the study groups, comparability of the groups, and ascertainment of exposure (equal method of recording outcomes). The scoring is done using stars with study of highest quality receiving 9 stars (Wells *et al.* 2003).

c) Observation studies (case series/reports) – the Joanna Briggs institute (JBI) critical appraisal tool for case series and case reports (Appendix H and J) was the chosen tool for assessing the quality of case series and case reports. The groups that developed the JBI tool found it to be acceptable and valid for use (Munn *et al.* 2020). The JBI tool has been used by many studies and is becoming a widely accepted tool for the appraisal of studies. However, the validity and reliability remains to be assessed due to its recent development (Singh *et al.* 2021; Wang *et al.* 2021; Mahumud *et al.* 2020; Harris *et al.* 2018; Zucchelli *et al.* 2018).

When using the JBI appraisal tool for case series, there are 10 aspects looked at: the presence of an inclusion criteria, reliable method of measurement, valid method of diagnosis, consecutive inclusion of participants, complete inclusion of participants, reporting of demographics and clinical information, clear reporting of results, reporting site demographics and appropriate statistical analysis (Munn *et al.* 2020; Moola *et al.* 2017). The responses can be yes, no, unclear or not applicable. The scale can then be used to score out of 10 where yes equals 1 point and any other response is a 0 as some authors have done and choosing a minimum number such as 7 for high quality studies (Wang *et al.* 2021; Yang *et al.* 2021), or it can just be looked at subjectively and judged to be of low, moderate or high risk of bias based on the responses and the

decision of reviewers (Munn *et al.* 2020; Mahumud *et al.* 2020). A high quality study would indicate an unlikeliness of future studies to contradict the results while the opposite is true for a low quality study

3.6.2 Reviewers

A total of six reviewers were recruited for their participation in in this systematic review. They were required to read and agree to a Memorandum of Agreement (MoA) (Appendix C). This memorandum outlined the process and procedure of the study, the requirements of the participants (reviewers), the timelines and how the reviewer's input would be required to be submitted. All reviewers were required to submit the MoA signed and emailed back to the researcher for record keeping.

The six reviews were separated into three groups with each group containing a PhD level researcher, a master's level researcher, and finally the researcher. This was done to reduce bias in the study, ensured an appropriate mix of academic, clinical and research experience was present in of the review groups, and ensured that there was involvement and experience in systematic reviews, publications or research supervision.
The reviewers consisted of the following:

- Reviewer A: MTech (Masters) Chiropractic, PhD Radiology.
- Reviewer B: D.C., MSc, PhD Paediatrics.
- Reviewer C: D.C., MSc, PhD.
- Reviewer D: MTech (Masters) Chiropractic.
- Reviewer E: MTech (Masters) Chiropractic, Dip: Sports Medicine.
- Reviewer F: MTech (Masters) Chiropractic.
- Reviewer G: BTech (Bachelors) Chiropractic (Researcher).

Table 3.4 Participating reviewers

Group Allocated	Reviewer	Qualification	Country	Research experience	Academic experience	Clinical experience	Professional association
1	Reviewer 1	PhD	Malaysia	X	X	X	
	Reviewer 4	Masters equivalent	South Africa	X	X	X	
2	Reviewer 2	PhD	USA	X	X		X
	Reviewer 5	Masters equivalent	Netherlands	X	X	X	
3	Reviewer 3	PhD	Norway	X	X	X	X
	Reviewer 6	Masters equivalent	UK	X	X	X	X
1-3	Researcher	-	South Africa				

Each reviewer was allocated their articles for their respective group as seen in Table 3.5, the appropriate scale(s), as well as an explanation on how to use the scale. These were emailed to the reviewers after the receipt of all the MoAs and allocation of reviewers to the review groups was done. A confirmation email was sent to ensure that they reviewers received the documents and whether they had any questions. These emails were sent individually to each reviewer to maintain reviewer blinding. This was done to ensure that the reviews were completed independently and thus reduce bias (undue influence) in the reviewers' outcomes.

Table 3.5 Study allocation

	Group 1	Group 2	Group 3
Study type allocation	1) n-RCTs	1) RCTs 2) Case series	1) RCTs 2) Case reports
Total number of articles allocated	3	9	8

3.6.3 Ethics

- Reviewers participated on a voluntary basis, with no coercion.
- Autonomy was dictated that reviewers were able to choose participation and their contribution was based on their own judgement, experience and training, with no input from any other party.
- Justice – all reviewers were treated equally, based on the agreements made through the MoA (Appendix A). Should conflict arise in the review submissions a neutral arbitrator would have been appointed to adjudicate.
- Beneficence – the reviewers were able to contribute to the greater good of the profession with the contribution and be recognised should they wish to participate in the publication of the work in a peer review journal.

- Non-maleficence – this was upheld in this research as the contribution of the reviewers remained confidential and was reported in a collective report that does not reveal the identity of the reviewer. This ensured that there was no discrimination towards the reviewer by peers or others that may not agree with the review outcome. Should the research be published the reviewers can elect to participate as co-authors. Should they feel that this would be prejudicial to them, then they can also elect not to participate in the publication process.

3.7 DATA EXTRACTION PROCESS

Firstly, the reviewers completed their reviews with the relevant scales provided to them and were requested to submit their results to the supervisor. Once the researcher had completed his reviews, then access was granted by the supervisor to the reviewer reviews for the researcher to tabulate the results. The results were tabulated according to the criteria of each scale and recorded so the results of all three reviewers per articles was together. The results were than evaluated for any difference between the results of reviewers and to record a final score based on the overall results. The final score was based on the consensus of the majority and did not require statistical analysis.

Next, the researcher recorded the following information from each article:

- Form of measurement.
- Frequency of measurement.
- Duration of study.
- Number of participants.
- Blinding of assessors.
- Use of control.
- Randomisation of participants.

This information was recorded in a table followed by the limitations and clinical outcomes of the studies. Finally, the clinical outcomes of the studies were discussed while also considering the methodological quality of the study to give a final verdict.

3.8 DATA SYNTHESIS

Following the completion of the review process in Sections 3.5 and 3.6, the articles In Chapter Five were then grouped into categories according to intervention (e.g., manipulation and mobilisation), and then finally according to region treated (e.g. spine, hand, shoulder and TMJ). They will then be assigned to levels according to the description by Haldeman and Dagenaes (2012) and foley *et al.* (2003) with the highest level of evidence being Strong and the lowest level of evidence being none with additional from foley *et al.* (2003) being consensus and conflicting. These sources were chosen because of their development for a similar clinical application with Haldeman and Dagenaes (2012) being for manipulation and Foley *et al.* (2003) being for shoulder rehabilitation in stroke patients.

The addition of Foley *et al.* (2003) is due its levels of evidence also allowing for the consideration of n-RCTs and observational studies. the levels of evidence given for each category will provide a benchmark for practitioners to evaluate the use of mobilisation and manipulation on different areas in clinical practice.

Chapter Five discusses the above method of grading relating to each area of treatment which can provide practitioners with an idea of the level of evidence available for the treatment of OA using manipulation and mobilisation in the respective areas.

3.9 CONCLUSION

Chapter Three provided the methodology that was used for the design of the study as well as the identification, search criteria and selection of studies relevant to this systematic review. it also shows the method of extracting evidence, analysis, contextualization of data from the studies. This chapter has also shown the foundation of what the next three chapters will be built upon.

CHAPTER FOUR RESULTS

4.1 INTRODUCTION

This chapter contains the overall ranking of all three reviewers for each study as well as a percentage agreement between reviewers for the items within the scales and the article as a whole. It also further looks at characteristics aside from the scale used for each study such as the form of measurement used, the frequency of measurement, duration of the study, number of participants, blinding of the assessors, the use of a control group, the randomization of the participants and finally all the limitation identified within each study. The outcomes are then discussed in with the limitations in mind to give verdict on how valuable the study in providing evidence.

4.2 DATA

4.2.1 Primary Data

The primary data represented the responses of the reviewers using the scales, the majority ranking which is the rating given by the majority of reviewers per criteria which is then added together giving the overall ranking of the article. A percentage agreement per criteria was also shown to show how similar the responses of the reviewers were with a final added percentage agreement at the end showing degree of consistency between reviewers using that specific scale. Reviewer agreement can be placed into the following categories: slight agreement 21%–40%, fair agreement 41%–60%, moderate agreement 61%–80% and almost perfect agreement of 0.81–0.99 (Berkman *et al.* 2013). This assists with evaluating the consistency of the review process.

4.2.2 Secondary Data

Secondary data was also used to gain a better understanding on topics related to systematic reviews, osteoarthritis, manipulation and mobilisation. Multiple sources were used to gain information in the form of books, journal articles and systematic reviews. The bulk of the information was gained through articles found online as well the Durban University of Technology online library, followed by books obtained from the Durban university of technology library.

4.3 ABBREVIATIONS

JBI: Joanna Briggs Institute
NOS: Newcastle Ottawa scale
n-RCT: Non-randomised controlled trial
OA: Osteoarthritis
RCT: Randomised controlled trial
VAS: Visual analog scale

4.4 RESULTS

The results have been separated in to RCTs, n-RCTs and case studies/ reports. Each separate section will have a small introduction with a table showing the articles that are covered in that section.

4.4.1 Randomized Controlled Trials

Randomized controlled trials were reviewed using the PeDro scale found in (Appendix D) with 11 articles falling under RCTs. The scale contains 11 criteria with 1 point being awarded to each fulfilled criteria giving an article a maximum score of 11.

Table 4.1 List of tables of RCTs found in this section

Tabulated feedback data	Analysis of articles	Author(s)	Year	Title
Table 4.2	Table 4.3	Bhanushali, V. Jagtap, V. Poovishnu, D.	2017	Effect of facetal joint mobilization in lumbar spondylosis
Table 4.4	Table 4.5	Copurgensli, C. Gur, G. Tunay, V. B.	2017	A comparison of the effects of Mulligan's mobilization and Kinesio taping on pain, range of motion, muscle strength, and neck disability in patients with Cervical Spondylosis: A randomized controlled study
Table 4.6	Table 4.7	Huang, Z. Chen, J. Qi, W.	2009	Clinical research on treatment of vertebroarterial type of cervical spondylosis with 5-step manipulation and traction
Table 4.8	Table 4.9	Igatpurikar, P.	2013	Effect of Maitland Spinal Mobilization Therapy Versus Conventional Therapy in Lumbar Spondylosis with Radiculopathy
Table 4.10	Table 4.11	Maicki, T. Bilski, J. Szczygieł, E. Trąbk, R.	2017	PNF and manual therapy treatment results of patients with cervical spine osteoarthritis
Table 4.12	Table 4.13	Sharma, A. Alahmari, K. Ahmed, I.	2015	Efficacy of Manual Therapy versus Conventional Physical Therapy in Chronic Low Back Pain Due to Lumbar Spondylosis. A Pilot Study
Table 4.15	Table 4.16	Vieira-Pellenz, F. Oliva-Pascual-Vaca, A. Rodriguez-Blanco, C. Heredia-Rizo, A. Ricard, F. Almazán-Campos, G.	2014	Short-Term Effect of Spinal Manipulation on Pain Perception, Spinal Mobility, and Full Height Recovery in Male Subjects with Degenerative Disk Disease: A Randomized Controlled Trial
Table 4.17	Table 4.18	Villafane, J. Cleland, J. Fernandez-de-Las-Penas, C.	2013	The effectiveness of a manual therapy and exercise protocol in patients with thumb carpometacarpal osteoarthritis: a randomized controlled trial.
Table 4.19	Table 4.20	Villafañe, J. H. Silva, G. B. Bishop, M. D. Fernandez-Carnero, J.	2012	Radial nerve mobilization decreases pain sensitivity and improves motor performance in patients with thumb carpometacarpal osteoarthritis: A randomized controlled trial
Table 4.21	Table 4.22	Villafañe, J. H. Silva, G. B. Diaz-Parreño, S. A. Fernandez-Carnero, J.	2011	Hypoalgesic and motor effects of Kaltenborn mobilization on elderly patients with secondary thumb carpometacarpal osteoarthritis: A randomized controlled trial.
Table 4.24	Table 4.25	Villafane, J. H. Silva, G. B. Fernandez-Carnero, J	2012	Effect of thumb joint mobilization on pressure pain threshold in elderly patients with thumb carpometacarpal osteoarthritis

Table 4.2 Feedback data of article 1: PeDro Scale

Author(s):	Bhanushali, V. Jagtap, V. Devi, P.					
Year	2017					
Title	Effect of facetal joint mobilization in lumbar spondylosis					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	No	No	No	No	100%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	No	No	No	No	100%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	No	No	No	No	100%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	No	Yes	Yes	66%
9	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”	Yes	Yes	Yes	Yes	100%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	No	Yes	66%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	Total Score	7/11	6 /11	6/11	7/11	
		Overall Percentage Agreement:				94%

Table 4.3 Analysis of article 1

Authors	Bhanushali, V. Jagtap, V. Devi, P.							
Year	2017							
Title	Effect of facetal joint mobilization in lumbar spondylosis							
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Overall Ranking out of 11	Total percentage agreement
Pain assessment using VAS Spinal movement measure with MST	Pain assessment using VAS was measured pre-test and post-test Spinal movement using MST was measure pre-test and post-test	Duration of study was not mentioned, assumed to be over one day	60 participants 31 female and 29 male. Group A had 30 participants with 15:15 male:female ratio Group B had 30 participants with 14:16 male:female ratio	Assessor or therapist blinding was not mentioned	Control group: received TENS and MILT Study group: received Facet joint mobilisation, TENS, and MILT.	Randomization was mentioned in the study. But the method of randomization or sourcing of the volunteers was not mentioned.	7	94%
Limitations	The location of the research at the Physiotherapy College, suggests that these patients may have been patients attending the clinic(s) associated with the physiotherapy training. This may result in all participants being familiar with the interventions through pre-study treatment. This background may influence the study in that the participants may come to the study with preconceived notions of intervention effect or effectiveness. Additionally, from a treatment vantage point pre-study treatment without a washout period prior to study entry may negatively influence the study (through floor or ceiling effects) (Akobeng 2008). The patient inclusion criteria was very broad, with age (between 40 – 60 years) being the only determinant of inclusion. This implies that there is a possibility for non-homogeneity between individual patients and between the groups being compared (Mahue *et al.* 2006), given the wide clinical variation of OA. Participants were excluded if the low back pain was due to a tumor, acute ligament injury, a fracture, lumbar spinal surgery, osteoporosis, spinal injury or radiculopathy; some of which may be caustuve agents for OA or part of the clinical presentation of spinal OA. This would therefore negatively impact generaliseability of results to all spinal OA patients. From the study outline, it is also clear that there was no control for the use of medication (or its impact recorded) and finally it is unclear as to whether the patients were acute, acute on chronic or LBP chronic sufferers as these all impact the potential outcomes of the intervention (Mahue *et al.* 2006; Akobeng 2008; Valdes *et al.* 2017). To counter the above assertions, the study did present baseline characteristics of the participants comparing age, gender and the chosen outcome measures which showed the groups to be homogenous. But it did exclude patient occupations which may affect the clinical results (Dulay *et al.* 2015; Mahue *et al.* 2006). Further, this study made no mention patient naivety (given the context of recruitment), which influences patient response to treatment based on preconceived notions as opposed to actual response in a patient with no prior history with the intervention. This bias affects the impact the results present with clinically (Akobeng 2008). It was noted that random allocation was used, but the method of randomization was not mentioned nor was it mentioned whether the allocation of participants was concealed. This may suggest possible elements of research / researcher bias negatively affecting the study and its outcomes (Kendall 2003). Sample size or power calculations where not presented, so it is unclear whether the included participants outcomes would have been able to attain results that were better than chance alone (Christley 2010). To confound this further, there was no indication if dropouts. The implications for statistical analysis and conclusions that are drawn if the study is under powered is that the probability of type 1 (false positive) and type 2 error (false negative) occurring [is greater]. This means that statistically significant results or the lack of results may actually be false due to the small sample size (Christley 2010). The application of lumbar mobilisation was not clearly described (thus reducing replication of the study) in terms of patient position and mobilisation type (grade) was not clear. This also implies that the treatment protocol could not be extrapolated clinical patients in practice (and spinal regions outside of the lumbar segment(s) that were chosen in this study) (Kendall 2003). Therefore, it cannot be said that a specific intervention will have a specific outcome on a specific location of the low back, remainder of the spine or on a specific joint. This therefore suggests that there may be variable clinical outcomes (with outliers potentially skewing results), given the variability of patient presentation and variance in application of the intervention) (Kendall 2003).							

	Blinding of outcome assessors was not detailed which may have exposed the study to further bias due to potentially biased measurements (Renjith 2017). The outcome measures were found to be appropriate (Rothwell *et al.* 2005; Kendall 2003) and sensitive (Coster 2013) to the intervention and their relationship to the intervention was explained. The consistency of training of the therapists for both groups was not mentioned neither were the number of therapists, the persons responsible for screening or the consistency in training of the persons measuring the outcomes mentioned, which may further increase bias in the study (Kendall 2003). The length of the study was also not mentioned but is assumed to be over one day. The study also did not have any long-term assessment that showed if the changes lasted over a certain period of time or how long it took before previous signs and symptoms reappeared (if they did).
Outcome:	The authors reported that spinal mobilisation of the lumbar spine along with TENS and MILT was found to be more effective in pain relief and improving range of motion than either TENS or MILT alone. The experimental groups pre-test VAS score was 7.61 which improved to 2.47 post-test, while the control groups pre-test VAS score was 7.74 and improved to 6.4 post-test showing a 4 point difference between the groups with the experimental group having the largest improvement. Pre-test calculations showed no significant difference was found between group A (experimental) and B (control) with $p=0.6951$, whereas post-test, there was a significant difference between groups A and B ($p<0.0001$). When testing for change using the Modified Schobers test, the experimental group improved from 2.86 cm to 4.33 cm, while the control group improved from 2.89 to 3.20 showing a significant difference ($p<0.0001$) between the groups with the experimental group having a much better improvement in range of motion.
Discussion:	The factors that speak to the generalizability of the study results include that the participants came from the general population, the randomization of participants and measuring baseline characteristics of participants. The factors that negatively impact on the external validity include the broad inclusion criteria with age being the only inclusion criteria, lack of patient naivety, the lack of a washout period, not monitoring medication use, not stating the method of randomization and lack of concealed allocation, using a single therapist to treat both groups and not blinding the assessors. Considering all these factors the study was found to have a moderate to high level of bias suggesting the results of the study may not be exclusively related to the treatment but confounded by a variety of factors that were not controlled for. The above implies that the outcomes may not be replicatable in practice and possibly also in the research context. This would therefore require further research which addresses the short comings of this study (namely, small sample size, the lack of sample power calculation, and the intervention as well as outcome measurement being all performed over one day), in order to determine whether the results attained were and are indeed a direct measure of the intervention.
Conclusion	Based on the limitations discussed in this table, the study was found to have a moderate to high level of bias which impacts the external validity of the results. In contrast, the reviewers rated the article with an overall agreement of 7/11 indicating that it had a moderate to high level of methodological rigour. Given these outcomes the systematic review suggests that there is potentially limited to no evidence in support of the use of mobilisation of the lumbar spine alone as it was evaluated in a programme along with TENS and MILT in the treatment of patients with lumbar spine OA. In the future, studies that look to further this research should look at using a larger sample of participants, performing the intervention over a longer period of time and having a follow up period which can assess the short, intermediate and long term effects of the intervention in order to improve the clinical and practical outcomes for practitioners in their field.

Table 4.4 Feedback data of article 2: PeDro Scale

Author(s):	Copergensli, C. Gur, G. Tunay, V. B.					
Year	2017					
Title	A comparison of the effects of Mulligans mobilization and kinesio taping on pain, range of motion, muscle strength, and neck disability in patients with cervical spondylosis: A randomized controlled study.					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	Yes	Yes	Yes	Yes	100%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	Yes	No	No	No	66%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	Yes	No	No	No	66%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	Yes	Yes	Yes	100%
9	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”	Yes	Yes	Yes	Yes	100%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes	100%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	Total Score	10/11	8/11	8/11	8/11	
		Overall Percentage Agreement:				94%

Table 4.5 Analysis of article 2

Authors	Copergensli, C. Gur, G. Tunay, V. B.
Year	2017
Title	A comparison of the effects of Mulligans mobilization and kinesio taping on pain, range of motion, muscle strength, and neck disability in patients with cervical spondylosis: A randomized controlled study.

Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Ranking out of 11	Total percentage agreement
1. Visual analog scale: measure severity of pain 2. Universal goniometer: used to assess active range of motion 3. Manual muscle testing: to assess the strength of cervical muscles 4. Stabilizer pressure biofeedback unit: used to measure strength of deep cervical flexor muscles 5. Neck disability index (NDI): used to measure neck specific disability	All measurements were recorded at three intervals: at baseline (pre-test), at the completion of the three weeks of treatment (post-test) and at the one month follow up.	A three week treatment period with a further 1 month follow up period. Totalling to 1 month and three weeks	45 participants. Group 1: control group receiving (conventional rehabilitation) CR with 15 participants Group 2: KT + CR group with 15 participants Group 3: MM + CR group with 15 participants	Concealed allocation was performed. There was no mention of assessor or therapist blinding. Participant blinding is also unknown.	15 Participants Were in the control group which only received conventional rehabilitation There were two intervention groups, group 2 received MM + CR and group 3 received KT + CR.	Concealed Allocation was performed using simple randomization However, the method of simple randomization was unclear.	8	94%

Limitations	This study, like Bhanushali et al (2017), is also limited with regards to recruitment. The participants were drawn from the greater Ankara region with the study being carried out at the Bayındır Hospital, Sogutozu, Ankara in Turkey. This venue for the study indicates that the participants were most likely hospital patients, between ages of 40-60 who were diagnosed with cervical spondylosis by physicians 1-3 months before data collection and had neck pain longer than 30 days, VAS score of at least 2/10, had no treatment during previous six months and had no contraindications to mobilisation (e.g. spinal cord issues, malignancy, inflammatory arthropathies, trauma, fractures, surgery, history of neurological or circulatory disorders, whiplash or psychological conditions). Although these criteria seem fairly rigorous, the lack of clarity of the recruitment source of the patients (namely, single site, hospital, clinic or general public) decreases the likelihood that the sample can be generalized back to the general population (Kendall 2003). Medication use and monitoring was not mentioned before or during this study. The impact of medication on the condition may result in responses that are not only due to the intervention. This impact may be mediated by the type(s) of medication, dosage alterations and prescription changes, these all affect the half life, presentation in the body and combination reactions between medications which cascade effects on the OA presentation as well as the patient reported outcomes (Valdes *et al.* 2017). Similarly certain occupations have been found to promote OA progression such as work that involves squatting, bending, kneeling or loading (Dulay *et al.* 2015; Mahue *et al.* 2006). This study did not take in to account the occupation of the patients which in this case, participants who engage in manual type work will find less improvement compared to those not in manual work thus influencing the results (Dulay *et al.* 2015; Mahue *et al.* 2006). OA has been found to occur more often in females, in some cases, it can also progress faster in females. The lack of baseline comparison can lead to bias in the results from group to group depending on the difference of gender within them (Boyan *et al.* 2013; Kendall *et al.* 2003). As the authors did not compare baseline characteristics between groups other than their age, a lack of homogeneity between groups between all the other listed characteristics above may lead to bias. To complicate the lack of baseline comparison, it is also unclear how the simple randomization of participants was performed (Kendall 2003). With this study being conducted in a hospital environment it is likely that the participants may have been hospital patients (generally more severe OA and more likely to have been exposed to many different interventions). Therefore, patient naivety may be negatively impacted as patients have had exposure to the intervention and may thus respond to the intervention based on preconceived biases (Akobeng 2008). According the authors, the sample size was determined to be a minimum of 12 participants per group using a power of 80% and a confidence interval of 95% which means that the study was adequately powered to attain usable and applicable results (Christley 2010). However, the sample was still small which can increase the risk of false negatives or positives leading type II errors (Keirse and Hanssens 2000).

	Without clarity on there being only one therapist applying interventions to both groups, there was a possibility for a difference in doctor patient dynamics such as the therapist emphasizing a possible clinical outcome or giving extra care to the intervention group versus the control group (Ernst 2007). Touch therapy may have played a role in this study as touch in itself has an effect on patients, in this case the Mulligan's mobilisation group received more physical interaction than the conventional rehabilitation group or the conventional rehabilitation plus kinesiotaping group (Tabatabaee *et al.* 2016). Both these factors suggest that there may have been an intervention bias that may have impacted the outcomes of the study. There were three groups, the control group [conventional rehabilitation (CR) - hot pack, transcutaneous electrical nerve stimulation (TENS) and exercise]. The first experimental intervention was Mulligan's mobilisation with movement technique in addition to the CR. The second experimental intervention which was Kinesio Tape application (KT) in addition to CR. All three CR treatment methods as well as the KT were adequately described and could be reproduced in clinical practice / future research. In contrast, the Mulligan's mobilisation, its application to specific spinal level(s) and side(s) was not clearly mentioned. This implies that different levels may have been treated in the 12 patients that fell into the Mulligan's mobilisation group or directed by patient pain. All these factors limit external validity (Kendall 2003). This study also had no mention of assessor blinding which can be a cause for assessor bias, impacting the outcomes measures. Non blinded assessors especially in judgement dependent outcomes such as muscle testing and stabilizer pressure biofeedback unit, can result in exaggerated or deflated results dependent on the stance that the assessor has toward the intervention (Moustgaard *et al.* 2014). The outcome measures by contrast were clear, appropriate and their relationship to the treatment intervention were also made clear. However, their relationship with treatment intervals was less clearly articulated and motivated for. Lastly the application of the mobilisation within a programme setting does not allow for clear identification of the impact of the mobilisation specifically.
Outcome:	The authors found that both Mulligans Mobilisation (MM) plus conventional rehabilitation or KT taping plus conventional rehabilitation were found to improve cervical range of motion versus conventional rehabilitation alone in patients with cervical spondylosis. All groups led to similar improvements in pain and muscle strength with. Outcomes that were measured were pain at rest, pain at activity, pain at night, muscle strength for neck flexion, neck extension, neck right lateral flexion, neck left lateral flexion, deep cervical flexors. In addition, active range of motion (AROM) of flexion, ROM of extension, ROM of right and left lateral flexion, ROM of right and left rotation and NDI score. Outcomes were significant in deep cervical flexion strength, ROM in extension and range of motion in right and left rotation ($p<0.05$). All other outcomes were insignificant ($p>0.05$).
Discussion:	The limitations of the study included, the lack of participant characteristics such as gender, occupation and severity or chronicity of condition. The seemingly single location sample source (older, more severe hospital patients), the small sample size of 45 with 15 in each group, and the lack of assessor blinding may all contribute in different ways to type 1 and type 2 errors. These limitations bring in moderate to high levels of bias which can significantly affect the results provided above. Given the moderate to high level of bias from the limitations discussed above, the results should be taken with caution. This is further complicated by the lack of clarity on the spinal level or levels that were chosen to use this intervention on as mentioned in the discussion so if applied in clinical practice or in future research, the practitioner would have to choose the levels themselves and outcomes could differ from this study because of that.
Conclusion	Considering the limitations of this study that impact on the external validity of the study implies that there is a moderate to high level of bias. In contrast, the reviewers rating for the internal validity of the study (8/11) indicated that the methodological rigour was of moderate to high quality. This suggests that collectively, there is a moderate to low level of evidence that MM plus CR or KT plus CR is better than CR alone at improving range of motion in the neck. There is however limited to no evidence available for only the mobilisation treatment procedure within the context of spinal OA of the cervical spine (viz cervical spondylosis). Thus, in future research, researchers investigating OA should look to obtain a sample from multiple sources and should detail their participant's characteristics according to gender, age, type of occupation and severity of condition. They should also clearly detail how the randomization has occurred, perform concealed allocation and blind the assessors to decrease the level of bias in the study. It is also important to explain the intervention performed as best as possible so the study is easily reproduceable and can be used easily in clinical practice.

Table 4.6 Feedback data of article 3: PeDro Scale

Author(s):	Huang, Z. Chen, J. Qi, W.					
Year	2009					
Title	Clinical Research on Treatment of Vertebroarterial Type of Cervical Spondylosis with 5-step Manipulation and Traction					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	No	No	No	No	100%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	No	Yes	66%
5	There was blinding of all subjects	No	No	No	No	100%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	No	No	No	No	100%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	No	No	No	66%
9	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”	Yes	Yes	Yes	Yes	100%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	No	Yes	66%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	No	No	No	66%
	Total Score	7/11	5/11	3/11	5 /11	
		Overall Percentage Agreement:				87.6%

Table 4.7 Analysis of article 3

Authors	Huang, Z. Chen, J. Qi, W.							
Year	2009							
Title	Clinical Research on Treatment of Vertebroarterial Type of Cervical Spondylosis with 5-step Manipulation and Traction							
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Overall Ranking out of 11	Total Percentage agreement
There was no mentions of what forms of measurement were used.	Not mentioned in the study	No mention of duration of study	120 participants in total (55 male and 65 female) Treatment group: 60 participants Control group: 60 participants	No mention of it in the study	A control was used made up of 60 participants who only received cervical traction. The intervention group received point pressing, muscle lifting, neck stretching, head turning, tapping and traction.	The study mentions randomly dividing participants in to group. But the form of randomization was not mentioned.	3	94%
Limitations	In a manner similar to Copurgensli et al (2017), this study was carried out at the Hospital of Peoples Liberation Army in Beijing and Wuhan. This location suggests that the participants were patients attending these military hospitals. This limits the generalizability of results back to populations (Kendall 2003). The inclusion criteria of the study required that patients met the diagnostic criteria for vertebroarterial type of cervical spondylosis (grading not provided) and it as unclear whether participants presented with acute, acute on chronic or chronic spondylosis. Patients were excluded if under 20 years of age or over 70, if they have severe disease of the brain, heart, blood vessels or kidney or if they cannot continue through out the treatment. As a result the type and presentation of the patients in this study had the opportunity to be very varied, however to the authors credit the pathogenesis seems limited to between two to six months (Mahue *et al.* 2006) providing some homogeneity. Similarly, homogeneity was attained through participants requiring aggravation of their headache, dizziness or tinnitus when their neck was rotated and/or extended. Additionally pressure on the intervertebral foramena and brachial plexus nerves resulted in a positive traction response and finally a radiograph had to show hyperosteogeny, narrowed intervertebral spaces, narrowed intervertebral foramen, displaced vertebra and abnormal cervical curve. Lastly, a rheoencephalogram or transcranial color-coded duplex sonography had to show deficient blood supply through the vertebral artery. Further consideration of confounding variables with regards to patient homogeneity (such as medication use, wash out period for other treatments) were not considered in the presented inclusion or exclusion criteria. For example the use of medication by participants was not controlled or mentioned which includes, dosage, type, or changes in prescription during the study (Valdes *et al.* 2017). The participant's occupation, which can affect the progression of spondylosis and thus effecting results, was not mentioned either although the location of the study suggests military personnel (Dulay *et al.* 2015; Mahue *et al.* 2006). Whether the patient had received a similar treatment or was naïve to the intervention recently was also not mentioned which can also negatively affect the outcome (Akobeng 2008). Notwithstanding the above two paragraphs the study indicates that at baseline there were no significant difference between the groups regarding age, sex and the condition's disease course, yet these details are not provided for verification. This lack of structural clarity is further delineated in the method of randomization and/or stratification and concealed allocation as they are not noted. The lack of creating homogeneity between the groups through inclusion/exclusion criteria, through randomization/stratification or appropriate concealed allocation can introduce bias as well as non-homogeneity between groups into the study (Mahue et al 2006; Kendall 2003), decreasing the study's ability to accurately measure the interventions impact on the condition and avoid type two error; this makes it difficult for the reader to make an informed decision as to the possible level of bias in the study and its impact on the outcome of the study (Kendall 2003). Given that the study has 60 participants per group, which may have adequately powered the study, but the lack of a sample size or power calculations does not confirm this. Thus all results need to be read with caution (Christley 2010; Kendall 2003).							

	The intervention(s) utilized were not completely described and technical jargon “muscle lifting” and “tapping” left he interpretation of the intervention to the reader. Thus the reproducibility of the research in research terms and in clinical practice is very limited, which implies that verification of the results of this study is not attainable (Kendall 2003). The intervention applied was also applied in a programme format, which does not allow for the extrapolation of the mobilisation outside of the other interventions. Additionally the confounding of the programme by the impact of touch therapy causing additional therapeutic effects in the experimental group as compared to the control group that only received traction therapy may have led to a “placebo type effect” (Tabatabaee *et al.* 2016) altering the outcomes in terms of them not accurately measuring the mobilisation intervention. There was also no mention if it was only one therapist that applied interventions to both groups as only having one therapist may lead to a difference in doctor patient dynamics where the therapists may have emphasized clinical outcomes to the intervention group versus the control group which may bias the results (Ernst 2007). The only outcome measurement that was found in this study was the final post-test measurement which measured the participants based on their grading of cured (signs and symptoms disappear, function restored to normal), remarkably effective (near to full improvement), effective (some signs, symptoms and dysfunction remain) or ineffective (no change). Then in contrast to the statistical analysis the authors state that several of the signs/symptoms had been “cured” after the treatment which they considered to be significant and had produced positive results for the patients. This is however limited by the lack of reporting on the specific signs and symptoms and seems to be at odds with the statistical reporting. Furthermore, this study made no mention of assessor blinding which increases the level of bias in the study, especially since there was only one outcome measure that was judgement dependant (Renjith 2017; Moustgaard *et al.* 2014). Ideally a study should contain more than one outcome measure and should have a balance of subjective and objective measures with tested reliability, validity and sensitivity to ensure outcomes are accurate and representative of clinical change directly as a result of the intervention (Moustgaard *et al.* 2014; Kendall 2003). Finally the authors did not mention how many times outcomes were measured and whether there were any follow up measurements that could indicate its short term or long term success and how these compared to seemingly missing baseline measures.
Outcome:	The authors suggest that according to their grading of cured (signs and symptoms disappear, function restored to normal), the intervention was reported as remarkably effective (near to full improvement), effective (some signs, symptoms and dysfunction remain) or ineffective (no change); that the results showed that the curative rate in the treatment group was 26.7% and the total effectiveness rate was 93.4% in the intervention group. In contrast, the control group resulted in a 13.3% curative rate and 86.7% total effectiveness rate. The authors concluded that the therapeutic effect in the treatment group was significantly improved compared the control group ($p<0.05$). However there is no published clinical significance (MCID) for the rating scale presented by the authors.
Discussion:	Although the authors concluded that there was a significant difference between the treatment group and the control group, limitations in this study introduced a high level of bias. Those limitations included, the lack of clearly detailed baseline characteristics between groups, apparent lack of randomization, no concealed allocation concealment, no assessor blinding, treatment was programme based and the form of measurement used was not explained. Participants were graded as, cured, remarkably effective, effective, or ineffective (no change), but the arrangements of symptoms as part of the outcome measures was not detailed. The study was found to have a high level of bias and the outcomes are thus not directly as a result of the intervention.
Conclusion	To conclude, due to the high levels of bias present in the study which was detailed in the limitations and discussion above, the external validity is very limited. This combined with the fair to poor overall reviewer rating (5/11) [indicating a poor methodological rigor] suggests that there is a low to no evidence in support of mobilisation in the context of vertebroarterial type of cervical spondylosis. Future studies should investigate this method treatment, to clearly describe the baseline characteristics, the outcomes as used in this study should be measured with multiple other outcome measures as well as the describe the programme and individual components of the intervention.

Table 4.8 Feedback data of article 4: PeDro Scale

Author(s):	Igatpurikar, P.					
Year	2013					
Title	Effect of Maitland Spinal Mobilization Therapy Versus Conventional Therapy in Lumbar Spondylosis with Radiculopathy					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	No	No	No	No	100%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	No	No	No	No	100%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	No	No	No	No	100%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	No	Yes	Yes	66%
9	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”	Yes	Yes	Yes	Yes	100%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes	100%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	Total Score	7/11	6/11	7/11	7/11	
		Overall Percentage Agreement:				97%

Table 4.9 Analysis of article 4

Authors	Igatpurikar, P.		Year		2013			
Title	Effect of Maitland Spinal Mobilization Therapy Versus Conventional Therapy in Lumbar Spondylosis with Radiculopathy							
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Ranking out of 11	Total Percentage Agreement
1. Pain on VAS scale 2. Spinal ROM using Schober's test 3. Straight leg raise test (SLR) 4. Oswestry disability index (ODI) scale for functional evaluation	Pre-test and post-test tests 30 days later	1 month	40 participants 20 in treatment group and 20 in control group.	No mention of assessor blinding	A control was used. Control group received conventional rehabilitation: lumbar traction, shortwave diathermy and core stabilization	Participants were randomized. Method of randomization was not mentioned	7	97%

Limitations	The study was carried out at the Kamala Nehru and Sancheti Hospitals, in Nashik, Maharashtra, India. This location suggestions that the type of patient entering the study was more likely a hospital patient (patient with more serious complaints), as compared to the general lumbar spondylosis patients. This is re-enforced by the inclusion criteria for this study, which required 45-60 year old patients, diagnosed with lumbar spondylosis and radiculopathy and having a pain rating of 6-10/10 on the visual analogue scale. Within this context however, the authors fail to mention how the lumbar spondylosis with radiculopathy was diagnosed and whether the method of diagnosis was a reliable method (i.e. a grouping of clinical sign(s) and/or symptom(s) or just a case history or both). This may be contrasted with the specific exclusion criteria which were spondylolysis, spondylolisthesis, spinal tumor, severe canal stenosis, spinal fracture, spinal surgeries, pregnancy, scoliosis and trauma. Yet in similarity to previous studies (Bhanushali *et al.* 2017 and Copergensli *et al.* 2017), medication and its effect on the outcomes of this study were not mentioned. Baseline characteristics suggested that even with the broad inclusion criteria, there was homogeneity between groups in terms of age, gender, duration of symptoms and occupation distribution. This does however not accommodate all the clinically important factors that affect the pathogenesis of spinal OA. The above is further compounded by the lack of randomization or participation concealed allocation methods which allows the reader to ascribe bias to these processes (Akobeng 2008). These biases include baseline differences between the groups, researcher bias and allocation bias (Akobeng 2008). These biases cannot be controlled by the small sample size which increases the risk of type 1 or type 2 error in to the study (Kendall 2003; Christley 2010). This is confirmed in that the publication has no supporting evidence of an *a priori* power calculation, to ensure that the sample would be able to provide outcomes with an 80% and at a 95% CI level to ensure that outcomes are indeed better than chance alone. In patient terms, the inclusion of hospital based patients, it is also feasible to consider the lack of naivety of the patients (who would have sought treatment various treatment options for their spinal OA) prior to inclusion into the study. This, along with the medication use would merit a period of washout in order to reduce the effects of these treatments on the outcomes. Also there is a consideration regarding the prior experience of patients with treatments as previous outcomes may cloud or colour responses to the research treatment. These concerns are related to the fact that when testing interventions, patient naivety needs to be accounted for. It is very important as the patients awareness of intervention applied to them may positively or negatively affect clinical outcomes based on the patient's prior experience of the intervention (Akobeng 2008). To the credit of the authors, the use of one therapist, provided consistency in terms of the intervention and the personal relationships with patients. However, this also has a downside, in that therapist's belief in one treatment over another may influence the patient's perception should one group have received more attention than the control group (Kendall 2003; Renjith 2017). One mechanism to limit therapist bias would be through an independent blinded assessor of measurement outcomes. This mechanism is however not alluded to by the authors (Renjith 2017). Finally the likelihood that the outcomes measured only the intervention is further reduced in that touch therapy may have also played a role in changes with the intervention group as the intervention group received more physical contact than the control group possibly effecting the results (Tabatabaee *et al.* 2016). The experimental group received a programme of Maitland spinal mobilisation from grade 1 to 4 with hot packs and core stabilization exercises. While the control group's programme was conventional therapy [short wave diathermy, intermittent lumbar traction and core stabilization exercises]. Therefore the outcomes of the study can at best only

	address the programme's effectiveness in relation to each other but not on any one modality within each of the programmes. This is further complicated by a lack of clarity on the number of sessions per week that the participants received as well as the specifics of each modality as it was applied at each session within the programme. Thus, although the authors indicated a positive treatment effect using these programmes, they need to be clearly detailed for the study to be applicable and repeatable in clinical practice and in future research (Kendall 2003). The choice of outcome measures by the authors were suitable for measuring changes in the patients using these methods of treatment and also contained a good mix of subjective and objective forms of measurement which included the VAS for pain, ROM of lumbar spine, straight leg raise and the Oswestry Disability Index (ODI) (Moustgaard *et al.* 2014). However, the values and measures were not adequately explained in terms of their application in relation to the treatment plan, for the results to be fully understood. Thus even though the results were reportedly positive, how these results where achieved and when cannot be effectively interpreted.
Outcome:	The conclusion reports that spinal mobilisation and conventional therapy had significant improvements in the straight leg raise test and disability index, but mobilisation showed better outcomes than the conventional therapy group in reducing pain and improving range of motion. Spinal mobilisation plus hot pack and core stabilization exercises VAS score pre-test was 7.55, Post-test was 1.45. SLR pre-test was 51.6˚, post-test was 94.5. ODI pre-test 3 graded as crippled, 11 as severe and 6 as moderate disability. Post-test all 20 graded as minimal disability. All outcomes measures gave a $p<0.05$ compared to baseline measurements, but there was no statistical significance found between the experimental and control groups ($p>0.05$) Conventional therapy group (SWD, ILT and core stabilization exercises) VAS score pre-test was 7.5, post-test: 2.05, SLR pre-test was 51˚, post-test was 91, ODI pre-test revealed 14 graded as severe and 6 as moderate disability and post-test all 20 graded as minimal disability. All outcomes measures gave a $p<0.05$ compared to baseline measurements. There was no statistical significance found between groups ($p>0.05$)
Discussion:	Based on the discussion above, in this table, there is a moderate level of bias (bias is shown in the lack of randomization description; lack of concealed allocation, patient naivety; lack of independent blinded assessor and use of one therapist with possible impact on patient perception of care). Finally, since only participants suffering with spondylosis of the spine with radiculopathy were used, the results will be limited to those type of patients. However the biggest limitation of the study as it is currently presented is that the outcome measures only measure the impact of treatment programmes and not individual interventions. Regarding the generalizability of the study (external validity), the sample homogeneity is questioned (particularly with regards to the variance of the pathogeneses of the diagnoses and impact of participant medication which was further complicated by a small sample size [increasing type 1 and 2 errors]. Additionally, with the impression that pateints were recruited from a hospital setting (indicating an increased likelihood of more severe OA patients). Finally because the study did not detail the individual treatments fully, did not explain the relationship of measures to treatment interventions and did not account for bias' from the therapist / blinded assessor vantage point; the specific impact of these on the outcome measures cannot be identified.
Conclusion	Based on the discussion in this table and how the limitations impacted the study, the review suggests that there is a moderate level of bias affecting the external validity. With respect to the internal validity, the reviewers ranked the study with an overall rating of 7/11, indicating that the methodological rigour as measured by the PEDro scale, indicates a moderate level of bias in the study. Thus, when considering both review analyses, this study has an overall moderate level of bias and thus the study provides moderate evidence in support of the two programmes tested in respect of improving the reported level of pain, lumbar range of motion, straight leg raise test and the reported disability levels of a patient with OA if the spine. The respect evidence for the use of mobilisation individually is limited to none due to it being a part of a programme. In future studies, randomization, concealed allocation concealment, and therapist and assessor blinding should all be addressed, whilst considering an increased sample size that considered a more homogenous sample that better represents the general spinal OA.

Table 4.10 Feedback data of article 5: PeDro Scale

Author(s):	Maicki, T. Bilski, J. Szczgiel, E. Trabka, R.					
Year	2017					
Title	PNF and manual therapy treatment results of patients with cervical spine osteoarthritis					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	Yes	Yes	Yes	Yes	100%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	Yes	Yes	No	Yes	66%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	Yes	Yes	Yes	Yes	100%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	No	No	No	66%
9	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”	Yes	Yes	Yes	Yes	100%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes	100%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	Total Score	10/11	9/11	8/11	9/11	
		Overall Percentage Agreement:				94%

Table 4.11 Analysis of article 5

Authors	Maicki, T. Bilski, J. Szczygiel, E. Trabka, R.							
Year	2017							
Title	PNF and manual therapy treatment results of patients with cervical spine osteoarthritis							
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Ranking out of 11	Total Percentage Agreement
1. Functional rating index 2. Modified McGill Pain Questionnaire	1. Pre-test (baseline) 2. Post-test (two weeks from baseline at completion of treatment) 3. 3 months later (long term effects)	3 months and 2 weeks. 2 weeks of treatment 3 months to allow for long term effects to take place.	80 participants. 40 participants in each group	The assessor was blinded from patient allocation	There were two experimental groups (one receiving PNF, and the other received Manual therapy). The authors did not mention if either was meant to be a control.	Participants were randomized	9/11	94%
Limitations	The patients were recruited from the greater Krakow area, Poland and treated at the out patient clinic possibly linked to the Jagiellonian University Medical College. This is unlike the prior studies (Copergensli *et al.* 2017; Huang *et al.* 2009) that recruited their participants from within a hospital setting. This may imply that the level of disease activity and subsequent care seeking behaviour is different between the participants in the prior studies and this study (Akobeng 2008). This implies that the outcomes of these studies may not be comparable to previous studies but may be more related to patients seen in clinical practice / pre-hospital care. The selection criteria were thorough including: 45-65 year old female patients with cervical pain (chronic pain >13 weeks) related to spinal degenerative changes which was confirmed with radiographs and no cognitive impairments affecting the patient providing full informed consent. Excluded were developmental malformations and acquired defects of the cervical spine, trauma to the cervical spine, cervical spine instability, osteoporosis, cervical myelopathy, signs of radicular symptoms and the use of painkillers, anti-inflammatories or muscle relaxants (the latter medications is a welcome consideration that many studies do not consider. This does however not fully include other systemic medications that may impact on outcomes. Items that were not considered in the above criteria include a specific NRS rating for inclusion, occupational impacts (Dulay *et al.* 2015) and patient naivety (Akobeng 2008), which may individually or collectively impact the results (Kendall 2003; Mahue 2006). Baseline comparisons between groups were also performed which considered age, BMI, and type of work which helps eliminate the possibility of type 1 and 2 error due to differences between groups (Assman 2000; Kendall 2003; Christley *et al.* 2010). Unlike previous studies, this study reports patient randomization by selecting a sealed envelope containing either an even number (PNF group) or an odd number (manual therapy group). Similar to previous studies, the authors neglect to mention if concealed allocation was implemented. The former assists with eliminating researcher bias in the group allocation process (Kendall 2003), but the latter does provide some concern about the allocation. The authors did not mention whether an *a priori* analysis was done before the study started to determine the sample size, so the statistical power of the study is unknown and may predispose to an increased probability of type 2 error (Christley 2010). This may be further increased through participant drop out or attrition bias. The drop outs may also impact the baseline similarities per group and thus the outcomes achieved by each (Akobeng 2008). The interventions were no outlined well, which prevents the study from being repeated in the future or being used in clinical practice (Kendall 2003). The use of only one therapist (not dissimilar to the previous study), may have resulted in therapist bias and its effect on patient perception of care and the outcome may have been amplified as the groups did not receive similar exposures to touch therapy (Tabatabaee *et al.* 2016; Ernst 2007). A study needs to contain a balance of both subjective and objective measure (Moustgaard *et al.* 2014). This study, however lacked any form of objective measurement (usually used to interpret subjective outcomes and help illuminate the effect of therapist bias or patient naivety bias or blinded assessor (Hawthorne) bias for example (Moustgaard *et al.* 2014). Given that this study had patients more like that of clinical practice, the impact of patient naivety may be similar between groups and its impact increases the likelihood of the measures actually increasingly measuring the interventions. But in contrast, no washout period was noted for any of the therapies included in this study, potentially negatively impacting the measurement outcomes (Akobeng 2008). A positive aspect of this study is that the outcome assessor was blinded, so they							

	could not influence the outcome measures directly of indirectly (e.g. Hawthorne effect or personal bias). Finally, they authors mentioned that their study evaluated the effects of the intervention in both short term (2 weeks after treatment) and long term (3 months after treatment, meaning the results are applicable up to 3 months post-treatment.
Outcome:	The authors found that both measures, at the post-test and three months later, indicated manual therapy and PNF had statistically significant ($p<0.0001$) improvements compared to baseline in the McGills pain questionnaire as well as the functional rating index which included questions on pain intensity, sleeping, personal care, travelling, work, recreation, lifting, walking, standing and frequency of pain. In the PNF group at post-test (after 2 weeks of treatment) and FU (3 months after treatment), significant improvements ($p<0.05$) were found in all outcome measures mentioned above compared to the manual therapy group except for walking, frequency of pain and personal care since those values were significantly different at baseline. Thus, PNF proved to be more effective than manual therapy. Functional rating index for PNF at pre-test was 16.06, post-test was 7.75 and FU was 9.03. Functional rating index for manual therapy pre-test was 17.94, post-test was 13.97 and FU was 14.89. McGill PNF pre-test was 10.47, post-test was 4.28, FU was 4.85. McGill in manual therapy pre-test was 13.93, post-test was 10.88, FU was 11.64.
Discussion:	The study and its external validity was impacted by lack of clarity on patient sample recruitment, lack of concealed allocation (researcher bias) and a lack of a washout period for the interventions and medicinal interventions. These were compounded by a lack of drop out reporting as well as the use of only subjective outcome measures. These factors are in and of themselves not significant considerations in terms of their impact on the outcomes, but collectively and in addition to the lack of an *a priori* analysis, they become significant in affecting the manner in which the data can be extrapolated to the general population. Thus the external validity is moderately compromised, suggesting that the impact of the possible bias on the results showing that both PNF and manual therapy were effective in improving function in participants with PNF being more effective, is negligible. Therefore the results can be accepted for female patients between ages of 45 and 65 and following within the criteria. The more pressing concern is the lack of intervention description which limits the ability of the reader to replicate the study in practice or research settings. Additionally the comparison of PNF to manual therapy cannot provide more than the relative effectiveness of one intervention over another as it does not provide evidence to say that either treatment is better than placebo.
Conclusion	The limitations of the study as mentioned in the discussion indicated a low to moderate level of bias, impacting the external validity. The reviewers gave the study an overall rating of 9/11 using the PeDro scale also indicating that there is a low to moderate level of bias in the study in respect of the internal validity. Considering these outcomes the study was found to have a moderate to high level of evidence in support of both PNF in a programme and manual therapy in a programme being effective in improving function and reducing pain in females between the ages of 45-65 suffering with OA of the cervical spine, with the caveat that it is not known whether either treatment is actually better than placebo. However, the level of evidence for us of manipulation alone is limited to none since manipulation was performed as part of a programme in this study. As a result future studies should aim to determine whether either or both the interventions are better than placebo, in order to contextualize the results obtained in this study. Additionally the studies going forward should not only address the short comings identified in this study, but also consider ways that would allow for the study results to be applicable to a greater proportion of patients within the general practice setting.

Table 4.12 Feedback data of article 6: PeDro Scale

Author(s):	Sharma, A. Alahmari, K. Ahmed, I.					
Year	2015					
Title	Efficacy of Manual Therapy versus Conventional Physical Therapy in Chronic Low Back Pain Due to Lumbar Spondylosis. A Pilot Study					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	No	No	No	No	100%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	No	No	No	No	100%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	No	No	No	No	100%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	Yes	No	Yes	66%
9	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”	Yes	Yes	Yes	Yes	100%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes	100%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	Total Score	7/11	7/11	6/11	7/11	
		Overall Percentage Agreement:				97%

Table 4.13 Analysis of article 6

Authors	Sharma, A. Alahmari, K. Ahmed, I.
Year	2015
Title	Efficacy of Manual Therapy versus Conventional Physical Therapy in Chronic Low Back Pain Due to Lumbar Spondylosis. A Pilot Study

Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Ranking out of 13	Percentage of agreement
1. Modified Schobers test – measuring extension, flexion and side flexion. 2. Oswestry Low Back Pain Disability Questionnaire 3. Visual analog scale for pain at rest and activity	Measurements taken twice. Once at baseline : Pre-test. And once after the last session of intervention after 4 weeks (post-test)	4 weeks.	30 participants. 14 females and 16 males, split in to two groups.	Not mentioned	The control group received conventional rehabilitation: Traction, Lumbar stabilization and Stretching exercises	Participants were randomized. However, the method of randomization was not mentioned.	7/11	97%

Limitations	The participants for this study were recruited through the Department of Medical Rehabilitation Sciences, King Khalid University, Saudi Arabia, and its associated clinic(s). This would suggest that patient recruitment is likely to involve patients with a longer standing condition or one that is more recalcitrant to care as the recruitment venue is not usually seen as a primary health care center but as a referral center with specialist care. In addition the criteria required patients between 40 and 70 years of age, with a history of insidious aching pain, limited lumbar range of motion of lumbar spine (with extension, flexion or lateral flexion), pain with standing and relieved with sitting, associated pins and needles/intermittent burning or numbness, but with no neurological deficits and radiological evidence of joint degeneration. Although the exclusion criteria were extensive and would have assisted in group homogeneity, there was no consideration of medication use (prior to the study and during the study). Chronic medication use for the low back pain or other systemic concurrent conditions may also lead to a difference in response to the intervention ultimately influencing the results between the groups (Valdes *et al.* 2017). The other area of concern is that of patient occupations/retirement/medical boarding and its impact on the homogeneity between the groups, as literature suggests that certain occupations are found to promote the progression of spondylosis/OA (Dulay et al 2015; Mahue et al 2006). Therefore, these factors may influence the ability of the study in measuring the ability to differentiate between the clinical improvements in each of the groups as a result of the intervention versus differences in homogeneity. It would therefore have been useful to have the study provide baseline measures of the major outcomes in the study as well as a comparison between the patient demographic and risk factors, but this was not reported. Thus, bias as well as increased chances of a type two error occurring in drawing the conclusions is more likely (Kendall 2003). This lack of homogeneity is compounded by a lack of concealed allocation and appropriate randomisation (Kendall 2003), but mitigated by the sample size having been calculated and determined to be 30 participants with a power of 80% and a significance level of 0.05 (Christley 2010). However, 30 participants for a study to be compared to a larger population still appears to be small to be properly generalized back to the population as there would still be a high risk of false positives and negatives with two groups of 15 participants (Keirse and Hanssens 2000). Given that the patients were drawn from a hospital setting in a specialist care facility it is likely that patients would have been exposed to similar treatment options as occurred in the study. No mention is made for the control of naivety and/or prior experience with care offered in this study. Therefore participant bias in the form of lack of patient naivety, patient preference for specific interventions and a lack of novelty of the interventions may impact the subjective outcomes which predominate in the study. This implies that reported outcomes were driven principally by past patient experience as compared to actual patient clinical improvement in the study (Moustgaard *et al.* 2014; Akobeng 2008). Further complications arise from the lack of a washout period prior to the study (in terms of prior interventions – including medication) which may impact the clinical outcomes reported and recorded separately from the actual intervention being tested.

	The manual therapy group received manual therapy and lumbar stabilization exercises [Maitland mobilisation described adequately; lumbar stabilization exercises not detailed]. The second group which received traction, lumbar stabilization and stretching exercises [with only the traction therapy detailed]. This limits study replication and verification of the results through research or in clinical practice (Kendall 2003). Without overt detailing, it was assumed that one therapist applied interventions to both groups, thus implying possible therapist influence on particularly the subjective outcomes based on the possibility of different doctor patient dynamics between the groups (Ernst 2007). Finally, touch therapy (having its own therapeutic effects) may also have impacted the outcomes as the intervention group received mobilisation which involved touch, whereas the control group did not have any form of physical contact (Tabatabaee *et al.* 2016). The outcome measurement tools were aligned with the interventions being tested and did measure them adequately, however, the authors could have used second objective method of measurement for the study to lower bias (Moustgaard *et al.* 2014), in addition to having a blinded assessor, to reduce assessor bias (Moustgaard *et al.* 2014). This study had no short term or long term follow up meaning the results are only relevant to immediate effects after treatment
Outcome:	The authors stated that that Group 1 (Maitland Mobilisation and lumbar stabilization exercises) showed significantly greater improvements in pain and Oswestry disability index compared to group 2 (traction, Lumbar stabilization and stretching exercises) ($p<0.05$). Both groups had improved in ROM (Extension, flexion and side flexion) after the 4 weeks compared to baseline ($p<0.05$), but there was no significant difference between the groups in ROM ($p>0.05$).
Discussion:	The conclusion of the study indicated that Maitland Mobilisation and lumbar stabilization exercises (group 1) provided significantly better results in pain reduction and ODI than lumbar traction, lumbar stabilization and stretches alone (group 2). The sample size, although small was calculated to have sufficient power to provide results that would provide a definitive outcome. However the lack of homogeneity between the groups (i.e. no baseline comparison and some critical factors not controlled for), means that the outcomes may actually not be measuring only the outcomes of the intervention but also the impact of these uncontrolled factors. Thus, this study was found to have a moderate, possibly high level of bias. This results from the homogeneity concerns (medication, naivety, large age range, occupational impact), the lack of concealed allocation, researcher bias, therapist bias, impact of touch therapy outweighing the positive impact of the extensive exclusion criteria, randomization and use of one assessor outweighing the randomization, use of multiple outcomes measures and the calculation of the power of the study. Thus the ability to generalize the outcomes of this study to the patient population in practice is at best problematic, given these concerns, but it is also complicated by the fact that each treatment group actually received a programme of care, thus it is not possible to determine the impact of any one intervention given that the interventions may have synergistic or antagonist effects within one group (thus either amplifying or negating the true clinical impact of any one of the individual interventions).e
Conclusion	Thus the impact of bias on external validity is moderate to high. In contrast, the internal validity, recognizing methodological rigour, was rated at 7/11 using the PeDro scale indicating that the study had a moderate to low level of bias. Therefore although the research design was fairly rigours, the implication for generalization is problematic. This tension always exists within the comparative paradigms of research and clinical practice. Thus the level of evidence available for the use of mobilisation as an intervention for spinal OA is low to none, given that the outcomes of this study was in a programme of care format as opposed in an individual therapy being tested. Therefore future studies would need to isolate the programme components to test individual clinical impact as well as the relationship (synergistic / antagonistic) between the interventions.

Table 4.14 Feedback data of article 7: PeDro Scale

Author(s):	Vieira-Pellenz, F. Oliva-Pascual-Vaca, A. Rodriguez-Blanco, C. Heredia-Rizo, A. Ricard, F. Almazán-Campos, G.					
Year	2014					
Title	Short-Term Effect of Spinal Manipulation on Pain Perception, Spinal Mobility, and Full Height Recovery in Male Subjects With Degenerative Disk Disease: A Randomized Controlled Trial					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	Yes	Yes	Yes	Yes	100%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	No	Yes	Yes	Yes	66%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	Yes	Yes	Yes	Yes	100%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	Yes	Yes	Yes	100%
9	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”	Yes	Yes	Yes	Yes	100%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes	100%
11	The study provides both point measures and measures of variability for at least one key outcome	No	Yes	Yes	Yes	66%
	Total Score	8/11	10/11	10/11	10/11	
		Overall Percentage Agreement:				94%

Table 4.15 Analysis of article 7

Authors	Vieira-Pellenz, P.T. Oliva-Pascual-Vaca, A. Rodriguez-Blanco, C. Heredia-Rizo, A. M. Ricard, F. Almazán-Campos, G.							
Year	2014							
Title	Short-Term Effect of Spinal Manipulation on Pain Perception, Spinal Mobility, and Full Height Recovery in Male Subjects with Degenerative Disk Disease: A Randomized Controlled Trial							
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Overall Ranking out of 13	Total Percentage agreement
1. Visual analog scale: Pain measurement of lower back pain (LBP) 2. Passive straight leg raise test (SLR) ROM 3. Spinal mobility in flexion FFD test (finger to floor distance test) 4. Stadiometer: measures height variations and amount of IVD compression	Pre-test and Post-test on the same day all within one hour.	1 day	40 participants. 20 in the Treatment group and 20 in the control group.	Assessors were blinded	A control was used. Control group received sham manoeuvre. Treatment group received spinal manipulation.	Participants were randomized using randomization.com	10/11	94%
Limitations	The study was conducted at a university-based physical therapy research clinic, linked to Department of Physical Therapy, Curitiba, Parana, Brazil. This study therefore seems to have patients that are not dissimilar to Maicki *et al.* (2017) where they were recruited from the general public to the clinic and were not hospital based as the prior studies (Copergensli *et al.* 2017; Igatpurikar 2013; Huang et al 2009). This provides an excellent base from which to generalize the results of the study, as the patients better represent those seen in clinical practice. The population in the study were men (18-55 years) with a body mass index (20-25kg/m2) and imaging evidence of disc degeneration (lumbosacral IVDs), with low back pain (no intensity requirement and with or without radiating pain to lower extremities above the knee). But unlike Igatpurikar (2013) who referred to and controlled for occupation, this study did not. Additionally as seems the trend in these publications, there was no control of the use of medication (administration, dosage, adherence or type) prior to entry into the study, during the study and during analysis, which may negatively influence the studies ability to actually note the clinical changes as a direct result of the intervention (Valdez *et al.* 2017; Mahue *et al.* 2006). The authors also did not record the duration the participants had LBP for, so they would be at different stage of chronicity. There was randomization of the participants, using an online random generator, limiting researcher bias, but there does not seem to have been concealed allocation balancing the bias in the study (Kendall 2003). Base line characteristics were taken before the intervention to confirm group homogeneity in terms of age, weight, height, LBP severity, SLR test and stadiometry, but not in respect of the medication use, LBP chronicity and other factors affecting homogeniety. Therefore although both groups may have the same physical characteristics, the mental, emotional and psychosocial factors influencing especially the subjective outcomes have not been accounted for. This is pertinent as the participants have also not been screened for treatment naivety / treatment novelty, which is important particularly when applying a sham intervention (Akobeng 2008). A calculated sample of 18 participants per group using a confidence level of 0.95 and a beta risk of 0.01 to detect a difference of equal to, or more than 17.5% difference in the between groups comparison of the stadiometry values. A standard deviation of 15% with 10% rate of loss to follow up was assumed which falls within what is necessary for a study to have adequate statistical power (Keirse and Hanssens 2000; Christley 2010). This implies that the study had an adequate sample for at least one outcome measure. The treatments (manipulation and sham), were not adequately described for purposes of replication in research or for the former in clinical practice (Kendall 2003). The manipulation procedure was referenced to tw previous studies (reference) as a “pull-move”, where the side lying torqued patient with the lumbar spine laterally flexed was short lever HVLA manipulated. The control group received the placebo/sham manoeuvre, which described the patient’s position being the same as the treatment group and that that no mechanical tension or manipulative thrust was applied. A Hawthorne effect may have played a role in influencing the outcome as there was only one therapist (Enrst 2007), in addition to the variance (as seen in touch therapy) in terms of the application of the HVLA manoeuvre as opposed to the sham/placebo (Tabatabaee *et al.* 2016).							

	The pre-post outcomes included low back pain severity using a VAS, passive straight leg raise range of motion, mobility of spine in flexion using finger to floor distance test and the stadiometer measuring height variations and the amount of IVD compression due to pressure on the spinal column. The preponderance of objective measures (3 types), is appropriate for this study and assists in negating undue influence related to patient perception, naivety and Hawthorne effects, given that they could account for such variables that may reflect in the subjective measure or VAS for low back pain. The negative aspect of multiple outcome measures means that either there is one assessor per outcome measure or these are multiple assessors that apply multiple outcomes measures. The former would negate the concerns related to consistency, reliability and validity of outcomes measures being applied in the same way, but the latter does not and introduces assessors' bias or error. The authors only state that evaluators collected and analyzed data and that they were blinded to treatment group allocation, but not the identified assessor roles. Therefore bias in outcome cannot be excluded. Finally outcomes from the intervention were measured immediately after the intervention providing no information on the intermediate or long term effects of the intervention.
Outcome:	In the conclusion the authors state that spinal manipulation to the lumbosacral joint in men with degenerative disc disease improved self-reported LBP, spinal mobility in flexion, hip flexion with passive SLR test and the height of the subject in the short term (Stadiometry) compared to the sham manipulation. In terms of values, the Treatment group: VAS (mm) decreased from 37.1 pre-test to 20.01 post-test ($p<0.001$). SLR test (degrees) increased from 39.1˚ pre-test to 52.75˚ post-test ($p<0.001$). FFD test (cm) decreased from 14.02 pre-test to 10.35 post-test ($p<0.001$). Stadiometry (mm) increased from -0.007 to 3.98 ($p<0.001$) compared to the control group: VAS (mm) no change 29.0 pre-test to 29.1 post-test ($p=1.00$). SLR test (deg) 48.05˚ pre-test to 47.59 ˚ post-test ($p=1.00$). FFD test (cm) 9.9 pre-test to 9.55 post-test ($p=0.008$) and stadiometry from -0.007 pre-test to 0.02 post-test ($p=0.142$). All outcome measures were significant when comparing the treatment group to the control group ($p<0.001$).
Discussion:	The study has enhanced generalizability, in that patients were recruited from the general public, inclusion and exclusion criteria was detailed, subjects were randomized in to groups, allocation was concealed, some participant characteristics were noted as similar at baseline, a relevant sham procedure was used, outcome measures were appropriate and power calculations were adhered to. In contrast, the limitations are associated with LBP chronicity and lack of medication control (lack of group homogeneity), patient naivety, lack of multiple assessor training or clarity on role as well as no mention of a washout period for pre-study treatments (medicinal or manual). Thus the external validity is potentially seen as moderate to fair.
Conclusion	Overall the reviewers rated the methodological rigour of the article 10/11 using the PeDro scale indicating that it had a low level of bias to internal validity. Considering that the external validity is seen as moderate, it is possible to consider that this article may be able to provide moderate evidence in support of the immediate effects of HVLA manipulation to the lumbosacral joint in men with degenerative joint disease resulting in improved self reported LBP, spinal mobility in flexion, degree of SLR test and a small increase in height of the participants compared to the sham intervention. Future studies that are looking to replicate and improve on this study need to consider having a larger sample of participants, include both woman and men, characterize the chronicity of the subjects condition, monitor or control medication use, clearly state the allocation concealment procedure and the treatment procedure, explain the assessor roles more clearly and finally assess the intervention outcomes with intermediate and long term follow up measurements.

Table 4.16 Feedback data of article 8: PeDro Scale

Author(s):	Villafane, J. H. Cleland, J. A. Fernandes-de-la-penas, C.					
Year	2013					
Title	The Effectiveness of a Manual Therapy and Exercise Protocol in Patients with Thumb Carpometacarpal Osteoarthritis: A Randomized Controlled Trial					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	No	Yes	Yes	Yes	66%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	No	Yes	Yes	Yes	66%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	Yes	Yes	Yes	Yes	100%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	Yes	Yes	Yes	100%
9	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”	Yes	Yes	Yes	Yes	100%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes	100%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	Total Score	8 /11	10/11	10/11	10 /11	
		Overall Percentage Agreement:				94%

Table 4.17 Analysis of article 8

Authors	Villafane, J. H. Cleland, J. A. Fernandes-de-la-penas, C.							
Year	2013							
Title	The Effectiveness of a Manual Therapy and Exercise Protocol in Patients With Thumb Carpometacarpal Osteoarthritis: A Randomized Controlled Trial							
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Ranking out of 11	Total Percentage agreement
1. Visual analog scale 2. Pressure pain threshold using a mechanical algometer 3. Grip strength using a grip dynamometer	4 times. 1. Pre-test 2. Post-test (after 1 month of treatment) 3. 1 month post intervention 4. 2 months post intervention	3 months	60 participants 30 in each group	yes	Yes Control group received inactive doses of pulsed ultrasound application of inert gel	Yes	10/11	94%
Limitations	Participants for this study were recruited from a nursing home in Collegno, Italy. This recruitment indicates that the results in the study may not be generalizable to all carpometacarpal OA patients as this group of patients is potentially older than the general OA population. This contrasts with those articles that recruited from the general population, allowing greater external validity (Maicki *et al*. 2017; Vieira-Pellenz *et al*. 2014). The study required participants to have a history of repetitive injury of their dominant hand (e.g. ex factory workers) and a diagnosis of stage 3 or 4 of the second carpometacarpal joint and OA of the dominant hand according to the Eaton-Littler-Burton classification (Eaton and Glickel 1987). Participants were excluded if they had a beck depression inventory score >4, or a state-trait anxiety inventory score >30, had a medical history of carpal tunnel syndrome, surgery to the first CMC joint, De Quervain tenosynovitis, neurological conditions (altered pain perception) or had received previous intervention for OA of the CMC joint. Participants with previous exposure to interventions treating their CMC joint because of OA were also excluded which prevents any participant bias and increases patient naivety to the intervention as previous knowledge of the intervention or a biased opinion of one intervention can lead to bias in the results (Akobeng 2008). In favour of this study and unlike previous studies (reference), this study required that medication use (analgesics, muscle relaxants or anti-inflammatory drugs) was restricted 24 hours prior to inclusion into the study, limiting the effect of medication on the outcomes (Valdez *et al.* 2014). Occupational impact on participants was also limited (e.g. factory workers) and dominant hand repetitively which allows for more homogenous groups thus improving outcomes measuring the interventions (Maheu *et al.* 2006). All participants had baseline measurements taken which included age, gender, pain on VAS, PPT, tip pinch and grip strength. These measurement revealed that groups where homogenous at baseline preventing any non-comparability and thus preventing bias (Boyan *et al.* 2013; Kendall 2003). Following baseline measurements, participants were randomized using a computer-generated method and allocated into two groups by an external assistant thus fulfilling the randomization process and concealed allocation adequately and preventing the possibility bias (Moustgaard *et al*. 2014; Akobeng 2008; Kendal 2003). The authors did not consider the effect of touch therapy or the placebo effect of the applied intervention versus the control group. Touch therapy is known to have an effect by itself on patients leading to a difference in results (Tabatabaee *et al.* 2016). The placebo effect could have taken place because of the difference in doctor patient dynamics in the control group and the experimental group. Since there was only one therapist, this can impact the results negatively (Ernst 2007). There was also only one therapist applying the treatments to both groups which could possibly lead to a difference in interaction dynamics such as the therapist emphasizing clinical outcomes in the experimental group vs the control group (Kendall 2003; Renjith 2017). In contrast, the treatment protocols were described adequately in all aspects which included all parts of the multimodal treatment intervention as well as the control group's intervention allowing for easy replication in clinical practice or in future research (Kendall 2003). The outcome measures chosen for the interventions were clear and appropriate and their relationship to the treatment interventions were clearly described. Although the study had objective and subjective outcome measures, the lack of a disability index measurement assessing impact on function and quality of life following the							

	intervention, would have assisted with contextualising improvements in addition to the VAS. This concurs with Moustgaards *et al.* (2014), who suggests a balance of subjective and objective measurements. Outcome assessors were also blinded to the allocation of participants which also assisted in reducing the level of bias in the study as participant and therapist blinding is not possible in this type of study (Renjith 2017). The follow up for the intervention was limited to two months after the intervention which the authors did not clarify whether they considered that short term intermediate follow up. But, because of the short follow up, results cannot be spoken about regarding long term affects.
Outcome:	According to the authors, patients with thumb carpometacarpal osteoarthritis who received the multimodal intervention had a significantly greater reduction in pain compared to the control group that received ultrasound therapy and was maintained two months after the intervention ($p<0.01$). However, there was no difference in the pain pressure threshold between groups except with the hamate bone ($p<0.05$ at post-test compared to control groups post-test) but was not maintained at one and two months follow up. The rest of the measures had no significant outcomes ($p>0.05$). Pain using the VAS, the experimental group had a pre-test of 5.0, post-test of 1.9, one month post-test of 1.5 and two months post-test of 1.5. Placebo group had a pre-test of 5.0, post-test of 4.9, one month post-test of 4.4 and two months post-test of 4.4. ($p<0.01$) between groups. PPT on hamate bone, the experimental group had a pre-test of 5.5 kg/cm2, post-test of 6.5, one month post-test of 6.0 and two months post-test of 6.1. Placebo group had a pre-test of 5.5, post-test of 5.5, one month post-test of 5.7 and two months post-test of 5.4. $p<0.05$ at post-test compared to control groups post-test. However at 1 month and 2 month follow up $p>0.05$.
Discussion:	The authors reduced the level of bias in the study through clear and specific inclusion and exclusion criteria, reporting base line measurements, randomizing participants, concealing participants allocation, controlling medication consumption 24 hours before examination, only including participants who were naïve to the intervention and blinding of outcome assessors. Those factors that may have impacted the study negatively through bias included, recruiting the participants from a nursing home, having a small sample size and having only one therapist to treat both the experimental and the control group. Based on these factors the study was found to have a low to moderate level of bias. This degree of bias will have impacted the outcomes making the reader having to accept the results with caution. The results would therefore also need to be applied with caution in clinical practice because the clear description of the intervention is hampered by the bias that was introduced making it unclear whether the positive clinical outcomes are only due to the intervention (and / or extraneous variables).
Conclusion	The impact of the bias on the external validity was found to be low to a moderate level. This mostly agrees with the internal validity of the study which was rated as 10/11 indicating a low level of bias. Overall, it can be considered that the article provides a moderate to high level of evidence in support multimodal method of treatment. However due to the treatment being in the form of a programme as opposed to an individual therapy being tested, the evidence in support of joint mobilisation as an intervention for OA is low to none. Future studies that look to replicate and improve on this study would need to isolate the programme components to give the individual clinical effect of treatment as well as the relationship between the interventions being tested. Additionally, future studies should also look to recruit participants from the general population, include another subjective form of measurement that measures function such as a disability index, an additional therapist to reduce therapist bias and measuring the long term effect of the intervention

Table 4.18 Feedback data of article 9: PeDro Scale

Table 4.18	Feedback data of article 9: PeDro Scale					
Author(s):	Villafane, J. H. Silva, G. B. Bishop, M. D. Fernandez-Carnero, J.					
Year	2012					
Title	Radial Nerve Mobilization Decreases Pain Sensitivity and Improves Motor Performance in Patients With Thumb Carpometacarpal Osteoarthritis: A Randomized Controlled Trial					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	No	Yes	No	No	66%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	No	Yes	Yes	Yes	66%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	Yes	Yes	Yes	Yes	100%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	Yes	Yes	Yes	100%
9	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”	Yes	Yes	Yes	Yes	100%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	No	Yes	66%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	No	Yes	66%
	Total Score	8/11	10/11	7/11	9/11	
		Overall Percentage Agreement:				87.6%

Table 4.19 Analysis of article 9

Authors	Villafane, J. H. Silva, G. B. Bishop, M. D. Fernandez-Carnero, J.
Year	2012
Title	Radial Nerve Mobilization Decreases Pain Sensitivity and Improves Motor Performance in Patients With Thumb Carpometacarpal Osteoarthritis: A Randomized Controlled Trial

Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Ranking out of 13	Percentage agreement
1. Mechanical pressure algometer: measures pressure pain threshold 2. Mechanical pinch gauge: measures pinch strength in a) tip pinch with index and thumb and b) Tripod pinch with index, middle fingers and thumb.	1. Pre-test 2. Post-test 3. 1 month follow up post-treatment 4. 2 months follow up post-treatment	3 months 1 month of treatment and 2 months for follow up	60 participants 30 in each group	Assessors were blinded	Control: intermittent ultrasound Experiment: radial nerve mobilisation	Participants were randomized	9/11	87.6 %

Limitations	The authors recruited the participants from the same location that Villafane *et al.* (2013) did, which was from the Department of Physical Therapy at the Extended Care Facility 3, Collegno, Italy, meaning they would not be similar to the general OA patients that present. This location suggests that participants would be much older and more advanced in disease due to being in extended care compared to the normal population that would present at clinical practice. The majority of the participants were woman, which would decrease applicability of the results to men suffering with OA of the hand in the clinical setting. Those included, presented with dominant hand pathology of the thumb CMC (OA) (factory workers and house workers). This was confirmed on radiographs according to the Eaton-Littler-Burton Classification (Eaton and Glickel 1987). Patients were excluded if they scored more than 30 on the State Trait Anxiety Inventory or more than four on the Beck Depression Inventory (these accounted well for the impact of pain sensitization), a history of carpal tunnel syndrome, arthritis, previous surgery on the trapeziometacarpal joint, de Quervains tenosynovitis and degenerative or non-degenerative neurological conditions where pain sensation is altered. Participants were between the ages of 70-90, but it was not mentioned if that was a part of the criteria or the end result of the recruitment. This obscured the ability to determine age homogeneity between the groups (Kendall 2003). Further complicating homogeneity, the authors did not control medication use as part of the inclusion / exclusion criteria, which may impact outcomes due to changes in dosage or prescription during the study altering the results (Valdes *et al.* 2017). A wash out period for non chronic medications and a request to sustain chronic medications without change during the study would have been more appropriate. In addition, prior exposure to a similar intervention or even complete naivety of patients to the intervention would have further reduced bias in the study (Akobeng 2008). Base line comparisons which confirms whether groups are homogenous is necessary to prevent bias to between groups. The characteristics that the authors in this study compared at baseline were age, sex, state trait anxiety inventory (STAI), Beck depression inventory (BDI), and the outcome measures mentioned that were used to detect changes. These characteristics are adequate to detect differences between groups regarding the outcome measurements, however it was inadequate for detecting homogeneity between groups regarding the chronicity and stage of disease (Boyan *et al.* 2013; Kendall 2003) Randomization of participants which is important to prevent allocation bias was performed in this study, but the method was not articulated by the authors. Method is significant as different processes are subject to different bias' (Kendall 2003). Additionally, lack of concealed allocation being noted may introduce allocation bias

	where the researcher may place a certain participant in a group to support specific outcomes (Kendall 2003). Since in the case of interventions involving rehabilitation therapy or use of hands, blinding of the therapist and participants is not possible, so the best that can be done is blinding the outcome assessors to reduce bias and enhance validity which the researchers have done in this study (Akobeng 2008; Renjith 2007). Interventions were well outlined to enable replication in future studies / clinical practice. Touch by itself has a therapeutic effect on patients, so since the control group did not involve any touch, It is unclear if the results obtained in the experimental group are from the intervention itself or from the touch therapy (Tabatabaee et al 2016). Outcome measures were well linked to the intervention, which implies that the measures were also appropriate for the interventions being tested (Kendall 2003). A significant concern is the lack of a table comparing the differences between groups as well as the differences from the pre-test all the way to the final follow up. It is acknowledged that there are graphic representations, but that may not accurately reflect changes seen in actual numerical values. Outcome measurements were repeated after the intervention was completed, one month following the completion and two months following the completion of the intervention to assess for immediate in addition to short term changes seen with this intervention. The authors however, did not state what the necessary length time was to see changes in the participants, nor did they mention whether their follow up measurements were considered short term in intermediate term follow ups which is important to indicate whether the follow up was adequate enough to notice changes. There was no subjective method of measuring such as VAS or disability index when there should be a balance of subjective and objective outcome measures within a study (Moustgaard *et al.* 2014). The sample size for the trial was small which can possibly expose the study to type two error (Keirse and Hanssens 2000). No *a prior* analysis was reported to support the sample size, this further supports the possible presence of type 1 or type 2 errors (Christley 2010; Keirse and Hanssens 2000). Participants in control groups tend to under report findings if they know they are in the control group (Moustgaard et al 2014). The attitude of the therapist with the participants can also play a large role in how effective an intervention is. In this case there was no therapist blinding, so the therapist may have shown more interest in the experimental group which can impact the results (Moustgaard *et al.* 2014; Ernst 2007).
Outcome:	The authors found that radial nerve mobilisation showed significant improvements in pain threshold of participants compared to the sham group that received intermittent ultrasound. There was also significant improvements in tip pinch and tripod pinch strength in the experimental group. The intervention increased PPT by 3.33 kg/cm2 in the trapeziometacarpal joint which was maintained throughout the first and second follow ups ($p<0.001$) compared to the placebo group. PPT in the scaphoid bone and hamate bone also increased but was not significant between experimental and placebo group ($p>0.05$). Tip pinch strength significantly improved ($p<0.05$) compared to the placebo group and tripod pinch strength increased by 2.83kg but was not significant between groups ($p>0.05$).
Discussion:	The study did well to limit bias in randomizing participants, blinding of all outcome assessors, comparing the groups at baseline for homogeneity and the use of more than one outcome measure. The negatives include increased bias due to lack of blinding of subjects impacting patient expectations; lack of therapist blinding; lack of a subjective measurements; not controlling medication use; using a washout period to exclude effects of previous therapies: lack of concealed allocation and using a control intervention not similar to the main intervention and including the effects of touch therapy. Thus, the study was found to have a moderate to high level of bias impacting outcomes negatively implying results need to be taken with caution. As the intervention was described adequately, it may be replicable in clinical practice and future research, but the limitations above decrease external validity and compromise expected outcomes.
Conclusion	The limitations of the study may have had a moderate to high effect on the external validity credibility of the outcomes. However, the reviewers rated the article with an overall rating of 9/11 meaning it had a low to moderate level of bias on internal validity, which does not agree with the level of bias based on the limitations found regarding external validity. Therefore although the research design was rigorous, the weakness of the external validity reduces generalizability the study can be assumed to have moderate to low evidence in support of radial nerve mobilisation for the treatment of patients with thumb CMC OA. Additional aspects that researchers who look to replicate and improve on this study include, recording the chronicity and stage of disease at baseline between groups for homogeneity, using a subjective outcome measure such as the disability index to measure change in pain and quality of life, concealing allocation and clearly stating the outcome values numerically.

Table 4.20 Feedback data of article 10: PeDro Scale

Table 4.20	Feedback data of article 10: PeDro Scale					
Author(s):	Villafane, J. H. Silva, G. B. Diaz-Parreno, S. A. Fernandez-Carnero, J.					
Year	2011					
Title	Hypoalgesic and motor effects of kaltenborn mobilization on elderly patients with secondary thumb carpometacarpal osteoarthritis: A randomized controlled trial					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	No	Yes	No	No	66%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	No	Yes	Yes	Yes	66%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	No	Yes	Yes	Yes	66%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	Yes	No	Yes	66%
9	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”	Yes	Yes	No	Yes	66%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	No	Yes	66%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	Total Score	7/11	10/11	6/11	9/11	
		Overall Percentage Agreement:				81.45%

Table 4.21 Analysis of article 10

Table 4.21	Analysis of article 10							
Authors	Villafane, J. H. Silva, G. B. Diaz-Parreno, S. A. Fernandez-Carnero, J.							
Year	2011							
Title	Hypoalgesic and motor effects of kaltenborn mobilization on elderly patients with secondary thumb carpometacarpal osteoarthritis: A randomized controlled trial							
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Overall Ranking out of 11	Total Percentage agreement
1. Pressure pain threshold (PPT) using mechanical pressure algometer 2. Pinch strength using mechanical pinch gauge 3. Grip strength using grip dynamometer	Outcomes measured 4 times. 1. Pre-treatment 2. Post-treatment: after 2 weeks of treatment 3. 1 week after treatment ended 4. 2 weeks after treatment ended	4 weeks 2 weeks of treatment and 2 weeks of follow up	29 participants 14 participants in the treatment group. 15 participants in the control group	Not mentioned in the study	A control was used. Control group received ultra sound therapy for 10 minutes. Treatment group received kaltenborn mobilisation	Participants were randomized using simple randomization	9/11	81.45%
Limitations	The authors indicated that the participants were recruited from the Department of Physical Therapy of an Extended Care Unit which depends on the local health authority of Collegno, Italy. This study therefore seems to have participants that are quite different to the rest of the reviewed studies who recruited from hospitals or the general public (Bhanushali *et al.* 2017; Sharma *et al.* 2015; Igatpurikar 2013). This study participants were aged between 70 to 90 and were predominantly not self sufficient which is the same as the 2 other previously reviewed studies (Villafane et al 2013; Villafane *et al.* 2012) To be included, participants were required to be between the ages of 70 to 90 years with secondary carpometacarpal (CMC) OA in their dominant hand with clinical history of more than 10 years, with retained cognitive ability, ex-factory workers, and housewives who commonly used their dominant hand. The diagnosis of the condition was based on medical history and radiographic diagnosis of stage three or four CMC OA according to the Eaton-Littler-Burton classification (Eaton and Glickel 1987). Participants were excluded if they had carpal tunnel syndrome, arthritis, surgical interventions on the CMC joint, de Quervain tenosynovitis and degenerative or non degenerative neurological conditions where sensation of pain is altered. The inclusion and exclusion criteria appeared to allow for adequate homogeneity between groups (Maheu et al 2006), which was confirmed for a limited number of baseline characteristics. A positive for the study was that group allocation was randomized using an online random generator. However concealment of allocation was not reported possibly introducing allocation bias into the study (Kendall 2003). An *a priori* calculation was not reported causing concern that the sample size was inadequately powered.This is further compounded by the use of non parametric statistics for group sizes of 14 and 15 participants respectively. This exposes the study to false negative or false positive results diminishing or inflating effect size through observed trends, which are actually not statistically or clinically significant (Keirse and Hanssens 2000; Christley 2010). There was no subjective outcome measures, which does not detract from the study, as the objective measures are generally seen as more reliable and are less influenced by patient preference (Moustgaard *et al.* 2014), treatment novelty (Akobeng *et al.* 2008), patient naivety (Akobeng *et al.* 2008) and the Hawthorne effect (Sedgwick and Greenwood 2015) But it does limit the ability of the study to understand the clinical implications and perceived patient improvement. Generally it is recommended that there should be a balance of subjective and objective outcome measures within a study (Moustgaard *et al.* 2014).							

	Assessor blinding was not reported, which can lead to bias due to the assessor unintentionally impacting the results (Moustgaard *et al.* 2014). Especially since all outcome measures were objective and the assessor was not blinded, this can occur easily and unintentionally. Both the intervention and the sham protocol were described adequately to be repeated in future studies and in clinical practice making this easily applicable (Kendall 2003). The measurements made were clear and its relationship to the intervention was also clear. The outcome measures were also appropriate for the type of intervention. The authors did not identify whether their measurements were considered to record short, intermediate or long term. However based on the length of follow up, the timeframe would be considered short term (final follow up was two weeks after the intervention). Finally, unlike the trial by Vieira-Pellenz *et al.* (2014) which contained only men, this trial only contained woman. The author mentioned that most cases of OA in the hand occurs in woman which is why the study only contained woman. However, these results will have no clinical relevance in the case of a male patient with OA of the hand or for OA in general (e.g. the previous studies that reviewed only spinal degeneration).
Outcome:	The authors found that pain pressure threshold on the CMC joint in the experimental group showed a significant improvement from pre-test 2.98 kg/cm2 to final follow up 3.84 kg/cm2 ($p<0.05$). The change in the sham group was not significant, pre-test 3.09 to final follow up of 3.57 ($p>0.05$). between groups, the difference was not significant ($p>0.05$). PPT on the scaphoid bone in the experimental group showed a significant difference between pre-test 3.61 and post-test 4.87 ($p<0.05$), but no significant difference at follow up periods ($p>0.05$). There was no significant changes in the sham group ($p>0.05$) and also no significant differences between groups ($p>0.05$). Tip pinch strength, tripod pinch strength and Grip strength all had insignificant changes in pre-test vs final follow up in both experimental group and sham group ($p>0.05$). There was also no significant outcome between groups ($p>0.05$).
Discussion:	The study authors did well in randomizing participants, recording baseline characteristics to confirm homogeneity between groups, using more than one objective outcome measure throughout, and making statistical comparisons between groups and clearly explaining them. The limitations of this study that would affect the level of bias in it include, the lack of allocation concealment and not clearly stating procedural issues around blinding. These factors indicated that the study had a mild degree of bias meaning that the results can be accepted but with caution. Given the level of bias identified, the results would be applicable in clinical practice, however, they would only apply to female patients over the age of 70 who are suffering with secondary thumb carpometacarpal osteoarthritis and do not fall within the exclusion criteria. Another factor that would limit its applicability is that the participants were from an extended care facility. Therefore extension into clinical practice needs to be approached with caution when explaining expected outcomes to patients.
Conclusion	The impact of the limitations and thus bias on the external validity is mild and contextual, the outcomes can only be accepted with caution within the designated population. The reviewers gave the study an overall rating of 9/11 using the PeDro scale for internal validity. With the low level of bias on the external validity the high PEDro score on the internal validity, this study was found to have moderate to high evidence in support of kaltenborn mobilisation on elderly patients with secondary thumb CMC OA. This evidence is however limited to increase pain pressure threshold (reduce pain). Impact on other outcomes measures require further studies on larger populations to attain the required power. Future research that may want to replicate this study should look at using a larger sample and taking the sample for the general population for more generalizable results. Using a subjective form of measurement may reveal a larger impact in changes in quality of life compared to the objective methods alone. The length of follow up should also be increased to know the long term effects of the intervention.

Table 4.22 Feedback data of article 11: PeDro Scale

Author(s):	Villafane, J. H. Silva, G. B. Fernandez-Carnero, J.					
Year	2012					
Title	Effect of thumb joint mobilization on pressure pain threshold in elderly patients with thumb carpometacarpal osteoarthritis					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
1	Eligibility criteria were specified	Yes	Yes	Yes	Yes	100%
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes	100%
3	Allocation was concealed	No	Yes	No	No	66%
4	The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes	100%
5	There was blinding of all subjects	No	Yes	Yes	Yes	66%
6	There was blinding of all therapists who administered the therapy	No	No	No	No	100%
7	There was blinding of all assessors who measured at least one key outcome	Yes	Yes	Yes	Yes	100%
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	Yes	Yes	Yes	100%
9	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”	Yes	Yes	Yes	Yes	100%
10	The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes	100%
11	The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes	100%
	Total Score	8/11	10/11	9/11	9/11	
		Overall Percentage Agreement:				94%

Table 4.23 Analysis of article 11

Authors	Villafane, J. H. Silva, G. B. Fernandez-Carnero, J.
Year	2012
Title	Effect of thumb joint mobilization on pressure pain threshold in elderly patients with thumb carpometacarpal osteoarthritis

Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Overall Ranking out of 11	Total Percentage agreement
1. Mechanical pressure algometer 2. Mechanical pinch gauge: tip pinch and tripod pinch 3. Grip dynamometer to measure grip strength	Measured 4 times 1. Pre-test 2. Post-test 3. 1 week post-test 4. 2 week post test	1 month total 2 weeks of treatment 2 weeks of follow up	28 participants 14 in the experimental group 14 in the control group	Yes	Yes The control group received intermittent ultrasound for 10 minutes Experimental group received mobilisation	Yes	9/11	94%

Limitations	The participants were recruited from a terminal care facility at the Department of Physical Therapy in Collegno, Italy, which is similar to the source of participants in the previous three studies performed by the same authors Villafane *et al.* 2013; Villafane *et al.* 2012; Villafane *et al.* 2011). However it is unlike some of the prior studies which recruited from the general public (Maicki *et al.* 2017; Vieira-Pellenz *et al.* 2014). This implies that the outcomes are highly contextualized in the population associated with this study. The inclusion criteria included participants between the ages of 70-90 years, had clinically diagnosed thumb carpometacarpal OA in the dominant hand for more than 10 years (at either stage 3 or 4 on the Eaton-Littler-Burton classification (Eaton and Glickel 1987), had preserved cognitive function and ex-factory workers or housewives who used their dominant often and in a similar manner. Participants were excluded if they had carpal tunnel syndrome, arthritis, surgery on the trapeziometacarpal joint (TMJ), finger spring, de Quervain tenosynovitis, and neurological conditions where pain sensation is altered. The authors did not address prior treatment exposure or concurrent treatment or medication (dosage, frequency, change, chronic or short term medication) and the cumulative effect of the intervention being tested or the impact participants preconceived ideas had on the intervention (Akobeng 2008; Valdes et al 2017). A washout period would have been helpful in this regard (Valdes et al 2017). The report of randomization (online random number generator) is positive as it prevents bias that may occur due to non comparability between groups which may affect results (Kendall 2003). Lack of concealed allocation does however mitigate gains from the randomization process (Akobeng 2008; Kendall 2003). A baseline comparison was performed between groups to assess for group homogeneity comparing age, sex and all assessment outcomes which adequately showed that both groups were homogenous therefore limiting the chance of type 2 error in the study (Boyan *et al.* 2013; Kendall 2003), which is positive. However the baseline was not compared for all possible nuances of patient presentation. It was stated that sample size and power calculation were performed using a significance level of 0.05 and a power of 80% which indicates that the study was adequately powered (Keirse and Hanssens 2000; Christley 2010), with a sample size of 14 per group. Finally, no drop outs were reported as stated by the authors. In terms of the interventions, touch therapy may enhance or detract from the interventions therapeutic effects being measured. Because the control and experimental groups differed in therapist interaction and handling, the effect touch therapy on experimental group may have affected the results (Tabatabaee *et al.* 2016). In addition the placebo and Hawthorne effects are also not excluded (Ernst 2007). The study also only had one therapist applying both treatments which can possibly lead to a difference in interaction dynamics by the therapist between the experimental group and the sham group such as giving extra attention to the experimental group or emphasizing the possibility of clinical outcomes which can affect the results (Kendall 2003; Renjith 2017). This latter is in part mitigated in that there were no subjective outcome measures; thus it would not be possible for under- or over-reporting their findings and thus clouding the impact of the intervention (Moustgaard et al 2014)

	The authors clearly described the both the experimental and the sham technique adequately including all important aspects of the treatment such as the positioning, the technique, the duration, the repetitions and any other important aspects that would be needed for the intervention to be repeated in clinical practice or in future research (Kendall 2003). Assessor blinding was implemented which helped reduce bias and increase the validity of a study (Renjith 2017). The measurements used were also clearly described, their relationship to the treatment were clear and they were also found to be appropriate for the intervention that was being assessed. Based on the duration of follow up (two weeks), the results seem to show the effect of the intervention in the short term, but this was not stated by the authors.
Outcome:	The authors concluded from the results that, participants suffering with secondary thumb carpometacarpal OA who received passive accessory mobilisation to the trapeziometacarpal joint had an increase in pressure pain threshold (PPT) (decrease in pain) compared to the group that received intermittent ultrasound (sham technique). Whereas tip, tripod pinch and grip strength did not change after treatment. The PPT in the TMJ for the intervention group at pre-test was 3.85 kg/cm2 and final follow up (FU) 4.74 ± 0.40 ($p<0.05$). The sham group at pre-test was 3.88 and final FU was 3.94 ($p>0.05$). Group by time interaction was $p<0.05$.The PPT in the scaphoid bone in the intervention group was pre-test 4.84 kg/cm2 and final FU 5.27 ($p>0.05$). The sham group was pre-test 5.03 and final FU of 4.96 ($p>0.05$). Group by time interaction was also insignificant ($p>0.05$). The PPT in the hamate bone for the intervention group was pre-test of 6.32 kg/cm2 and final FU of 6.58 ($p>0.05$). Sham group was pre-test of 6.41 and final FU of 6.16 ($p>0.05$). Tip pinch strength in the intervention group pre-test was 2.35 kg and final FU of 2.08 ($p<0.05$). The sham group was pre-test of 2.56 and final FU of 2.31 ($p>0.05$). Tripod pinch strength in the intervention group was pre-test of 3.01 kg and final FU of 2.65 ($p>0.05$). The sham group was pre-test of 2.56 and final FU of 2.31 ($p>0.05$). Grip strength in the intervention group was pre-test of 10.93 kg and final FU of 10.96 ($p>0.05$). The sham group was pre-test of 10.64 and final FU of 11.64 ($p>0.05$).
Discussion:	The study was well presented and limited bias by having clear inclusion and exclusion criteria, controlling the occupations of people that participated, randomizing the participants, comparing participants at baseline (although limited), and blinding the outcome assessor. The negatives of the study included lack of medication control / prior treatment control, lack of concealed allocation, not blinding subjects or therapists, not using any subjective form of measurement, and only using one therapist to treat both groups. Based on this, the study was found to have a low to moderate level of bias. This degree of bias will still allow the results to be accepted however with some caution. The results may be applicable in clinical practice and can be replicated in research because of the clear description of the intervention, but within the context of the highly defined population. The factors that will limit the applicability and generalizability of the outcomes are, the highly specific characteristics of the participants, their previous occupation and the high female predominance.
Conclusion	The limitations were found to impact the study in terms of external validity making the outcomes acceptable but subject to a low to moderate level of bias. The reviewers rated the methodological rigour 9/11 using the PEDro scale, indicating a low levels of bias which agrees with the limitations. The limitations and the reviewer rating suggests that there is a resultant moderate to high level of evidence arising out of the study. If this study was to be replicated in the future, additional things that should be considered is taking the sample from the general population, using a larger sample, including a subjective form of measurement such as a disability index as not all improvements can be found using objective measurements and controlling or at least recording medication use.

4.4.2 Non-Randomised Controlled Trials

The scale chosen to grade the three n-RCTs was the Newcastle-Ottawa scale (NOS) (Wells *et al.* 2011) found in (Appendix F). The NOS assesses the quality of a n-RCTs from the following aspects: selection of the study groups, comparability of the groups, and ascertainment of exposure (equal method of recording outcomes). The scoring is done using stars with studies of highest quality receiving a maximum of 9 stars (Wells *et al.* 2003).

Table 4.24 List of tables of n-RCTs found in this section

Tabulated feedback data	Analysis of articles	Author(s)	Year	Title
Table 4.25	Table 4.26	Egwu, M. O.	2008	Relative therapeutic efficacy of some vertebral mobilization techniques in the management of unilateral cervical spondylosis: A comparative study
Table 4.27	Table 4.28	Nicolakis, P. Burak, E. C. Kollmitzer, J. Kopf, A. Piehslinger, E. Wiesinger, G. F. Fialka-Moser, V.	2001	An investigation of the effectiveness of exercise and manual therapy in treating symptoms of TMJ osteoarthritis
Table 4.29	Table 4.30	Qayyum, S. Waqas, S. Asim, H. M.	2017	Outcomes of mechanical traction and manual therapy in C5-C6 cervical spondylosis for radicular pain relief

Table 4.25 Feedback data of article 12: NOS

Author(s):	Egwu, M. O.					
Year	2008					
Title	Relative therapeutic efficacy of some vertebral mobilization techniques in the management of unilateral cervical spondylosis: A comparative study					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
Selection	1. Is the case definition adequate?	1	1	1	1	100%
	2. Representativeness of the cases	0	1	1	1	66%
	3. Selection of controls	0	1	0	0	66%
	4. Definition of controls	0	1	0	0	66%
Comparability (two point allocation)	5. Comparability of cases and controls on the basis of the design or analysis	1	2	1	1	66%
Exposure	6. Ascertainment of exposure	0	0	1	0	66%
	7. Same method of ascertainment for cases and controls	0	1	0	0	66%
	8. Non-response rate	0	0	0	0	100%
	Total Score	2/9	7/9	4/9	3/9	
		Overall Percentage Agreement:				75%

Table 4.26 Analysis of article 12

Authors	Egwu, M. O.							
Year	2008							
Title	Relative therapeutic efficacy of some vertebral mobilization techniques in the management of unilateral cervical spondylosis: A comparative study							
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Overall Ranking out of 9	Total Percentage agreement
Pain status measurement - either pain free, some residual pain, fair improvement, pain was unchanged or pain was worse.	Only recorded after the intervention	4 weeks	96 participants 24 in each group	yes	There were 4 intervention groups for 4 different techniques	no	3/9	74%
Limitations	Participants were only recruited from one location, which were the patients that presented to a physiotherapy clinic and the manual therapy clinic associated with the Obafemi Awolowo University. The sample may be more related to patients seen in clinical practice / pre-hospital care which would help with generalizability of the population (Akobeng et al. 2008). This is similar to Maicki et al. (2017) where studies were drawn through the university clinic, but unlike other studies that were conducted in a hospital setting (Huang et al. 2009; Igatpurikar 2013; Copergensli et al. 2017). The study criteria required participants to be male, 40 to 50 years of age, diagnosed with cervical spondylosis associated with unilateral, severe neck pain (C5/C6 brachial symptoms) within six weeks prior to the study, a positive skin rolling test or digital pressure tests over these levels, with never having received manual therapy for neck pain and no history of contraindications for manual therapy in the region such as vertebra-basilar insufficiency, head or neck trauma, hypertension, active cancer, recent surgery, spinal cord damage or instability (Hutting et al. 2018; Kendall 2003). There was no control of medication use (dosage, frequency, change, acute versus chronic medication) (Valdez et al. 2018). Finally the sample contained male participants which restricts the applicability of the results to males only. The study lacked randomization or concealed allocation impacts negatively on the comparability between groups which introduces bias meaning the outcome may be due to reasons other than the intervention (Kendall 2003). Baseline characteristics (only age compared as homogenous) were not recorded which included occupation and pain levels before the study commenced which further confounds the ability to compare groups and reduce bias (Kendall 2003) and impact on the outcomes measures as being directly as a result of the interventions (Mahue et al. 2016; Dulay et al. 2015). The appropriate sample size and power of the study were not calculated which means it is unknown if the study underpowered or adequately powered which would indicate if the outcomes were true and not due to just chance (Christley 2010; Kendall 2003). Thus this study can only comment on trends. In terms of the intervention, it is noted that the placebo effect may have played a role as there was only one therapist (Renjith 2017; Ernst 2007). In contrast, touch therapy would not have caused differences between groups as the amount of physical contact was similar (Tabatabaee et al. 2016). The authors did however only include participants that were naive to the intervention which would help reduce participants bias as their awareness of the intervention may affect the results (Akobeng 2008). As for the intervention protocol description. The various techniques were described adequately but the author could have described the number of repetitions of oscillations per treatment session more clearly for it to be easily understood and repeated in clinical practice and in future research (Kendall 2003). There was only one therapist for all groups so there would be no problems with protocol consistency between groups. The study lacked a reliable form of measurement that had been tried and tested (Moustgaard et al. 2014). This single form of measurement was a subjective measure with five choices (pain-free, some residual pain, fair improvement, no change or worse), while there was no objective form of measurement measuring the outcome. This makes the study susceptible to bias from lack of homogeneity between the groups, placebo effect and other participant bias' (Moustgaard et al. 2014). Results were also only measured post intervention and had no measures to be compared back to (baseline measurements), meaning groups may have been non-comparable at the start increasing the							

	susceptibility of bias in the results (Kendall 2003; Mahue et al. 2006). Assessor blinding was seemingly not relevant as there was no baseline measurements from which to compare. Overall, the measurements were not clear, the outcome measure was non-specific to the intervention and a more appropriate form of measurement was needed for this study or at least an additional objective form of measurement (Moustgaard et al. 2014). The study also needed a control group that received either a sham intervention or the usual form of care to be compared to and to make the results comparable (Tabatabaee et al. 2016). Finally, the authors only assessed outcome at completion of intervention and measures were not repeated in a follow up period so these outcomes are only applicable to post intervention.
Outcome:	The Author found that using posterior anterior unilateral pressure (PAUP) and anterior posterior unilateral pressure (APUP) produced significantly more pain free participants than the cervical oscillatory rotation (COR) group and the transverse oscillatory pressure (TOP) group. The PAUP and the APUP groups also required significantly less treatment time to become pain free than the COR and TOP groups. The PAUP group had 11 pain participants pain free, 8 with some residual pain, 5 with fair improvement, 0 with no change and 0 worse. The APUP group had 15 pain free, 6 with some residual pain, 3 with fair improvement, 0 with no change and 0 worse. COR had 4 pain free, 9 with some residual pain, 8 with fair improvement, 2 with no change and 0 worse. TOP had 6 pain free, 8 with some residual pain, 9 with fair improvement, 1 with no change, and 0 worse. The number of pain free participants in the APUP and PAUP groups were significantly better than the COR and the TOP groups ($p<0.001$).
Discussion:	The study reduced bias with regards external validity with clear and specific study criteria as well as excluding participants who had received this intervention before. The factors that may have negatively impacted the external validity and increased bias were the convenience sample method, not randomizing or concealing allocation of participants, a lack of baseline measurements, one outcome measure that was subjective and recording outcome measures only once with no other measures to compare them to. These factors indicated that the study had a moderate to high degree of bias meaning the moderate results could only be accepted with a high level of caution. The outcomes are also difficult to apply to clinical practice / future research for multiple reasons. It is unknown if the sample had adequate power for results not to be attributed to chance, there was no control group so it would be difficult to generalize this to any population as its unknown how much touch therapy and the placebo effect may have played a role and the intervention needed more detail for it to be repeated. As for the study being replicated, the only factor limiting this is the description of the intervention protocol lacking some detail.
Conclusion	The limitations severely impacted the external validity of the interventions based on the reported outcomes indicating that there was a moderate to high likelihood of bias. The reviewers gave the study an overall rating of 3/9 using the NOS scale also indicating that the internal validity had a moderate to high level of bias. Considering both the external and internal validity, there is a resultant low to limited level of evidence arising out of the study that posterior anterior unilateral pressure (PAUP) and anterior posterior unilateral pressure (APUP) produced significantly more pain-free participants than COR or TOP. Problems that future studies would need to address is using a control group for the outcomes to be comparable, using reliable and valid outcome measures to accurately detect changes and following up on participants in the short and long term to show its effects over time.

Table 4.27 Feedback data of article 13: NOS

Author(s):	Nicolakis, P. Burak, E. Kollmitzer, J. Kopf, A. Piehslinger, E. Wiesinger, G. Fialka-Moser, V.					
Year	2016					
Title	An Investigation of the Effectiveness of Exercise and Manual Therapy in Treating Symptoms of TMJ Osteoarthritis					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
Selection	1. Is the case definition adequate?	1	1	0	1	66%
	2. Representativeness of the cases	1	1	0	1	66%
	3. Selection of controls	0	1	0	0	66%
	4. Definition of controls	0	1	0	0	66%
Comparability (two point allocation)	5. Comparability of cases and controls on the basis of the design or analysis	1	2	1	1	66%
Exposure	6. Ascertainment of exposure	0	0	0	0	100%
	7. Same method of ascertainment for cases and controls	0	1	0	0	66%
	8. Non-response rate	0	0	0	0	100%
	Total Score	3/9	7/9	3/9	3/9	
		Overall Percentage Agreement:				75%

Table 4.28 Analysis of article 13

Authors	Nicolakis, P. Burak, E. Kollmitzer, J. Kopf, A. Piehslinger, E. Wiesinger, G. Fialka-Moser, V.							
Year	2016							
Title	An Investigation of the Effectiveness of Exercise and Manual Therapy in Treating Symptoms of TMJ Osteoarthritis							
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Overall Ranking out of 9	Total Percentage Agreement
1. Pain at rest: using visual analog scale (VAS) 2. maximal experienced pain during last 2 days: VAS 3. overall impairment in daily life activities (chewing, speaking, yawning) using VAS 4. incisal edge clearance in mm 5. perceived improvement of jaw pain on 7 point scale	Measured 4 times. At baseline, before treatment, after treatment and six months follow up.	13 months with 6 months follow up period Maximum of 4 months control period with a mean duration of 35 days and a minimum of 5 days Maximum of 3 months treatment, a minimum of 10 days with a mean treatment period of 46.5 days	20 participants 18 female and 2 male	Blinding of assessor is not needed as it is a pre-test post-test study	There was only one group which acted as the control group and then participated on the treatment.	none	3	75%
Limitations	The sample was recruited from the Department of Dentistry at the University of Vienna, thus the study participants were taken from only one location and constituted of participants suffering with craniomandibular disorders which makes it difficult to generalize the outcome back to the population with general OA (Knapp 2016; Akobeng 2008). The inclusion criteria required radiological signs of osteoarthrosis of the temporomandibular joint (TMJ), with TMJ pain for at least three months, with no mention of exclusion criteria. Thus the inclusion criteria were very broad, not limiting age, previous injury, previous surgery, recurrence of pain (recovery differs with someone suffering for 20 years versus three months (Akobeng 2008), having received a similar form of treatment previously (patient naivety) and lack of monitoring or control of medication. This negatively impacts on whether the outcome measure actually measure the impact of the intervention (Kendall 2003; Akobeng 2008; Valdes *et al.* 2017). It has also been found regarding single group pre-test post-test studies that participants tend to improve in scores on subsequent use of measures or tests due to familiarity with the format, leading to a false assumption regarding the effectiveness of the intervention (Glass 1965). Although no intervention occurred in the control phase, external factors (e.g. uncontrolled patient characteristics or simply natural history) may have resulted in changes found (Knapp 2016). It was not reported as to whether participants were randomized or concealed allocation was used. This would mean that the comparison and generalization to other patients or populations would be almost impossible (Knapp 2016). The authors recorded baseline characteristics which included gender (18 females and 2 males), age (mean 48.8 ± 14.9), Chronicity of symptoms (mean of 2.7 years), as well as the measured outcomes. The sample size and power of the study was not calculated which means the study may be underpowered meaning outcomes may actually be due to chance (Christley 2010; Keirse and Hanssens 2000).The sample size was also small which increases the risk of false negatives (type 2 error) and may exaggerate / deflate the actual size of the intervention effect respectively (Keirse and Hanssens 2000). The study lacked a control group which severely limits the ability to control for the outcomes achieved especially for external causes that can influence the outcome measures and the bias associated with a clinical interaction (Knapp 2016). This is compounded in that the exact method of treatment and rehabilitation was not detailed in the study which makes it impossible to replicate in clinical practice or in future studies (Kendall 2003). They mentioned what method and techniques were performed on the participants, however, they did not mention how they were performed, the number of repetitions, progressions, sets and							

	duration of each technique. Aspects that would further increase bias in to the study is the placebo affect because of doctor patient dynamics or touch therapy which could not be controlled for (Ernst 2007; Tabatabaee *et al.* 2016). Assessor(s) blinding was not reported, which could lead to assessor bias where the assessor unintentionally underreports the results in the pre-test period or exaggerates the results in the post-test period (Renjith 2017; Moustgaard *et al.* 2014). In contrast, the outcome measures were found to be appropriate, clear and contained both objective and subjective methods of measurement which allowed for a better understanding of the effects of the intervention (Moustgaard *et al.* 2014). Finally, the authors followed up on the participants six months later to assess the length of the effects from the treatment period, but they did not mention whether they considered this to be intermediate or long term, however because it was six months it is assumed to fall under intermediate-long term follow up. This delayed measure does however suffer from memory recall bias in patients (Brusco and Watts 2015), in addition to the fact that there was no control for external influencers during this time lapse between the last treatment and the six month follow up measure, which further introduces bias (Akobeng 2008).There was a single participant who was excluded from the 6 months follow up since they were referred for splint therapy due to a lack of improvement in incisal edge clearance, but they experienced pain relief. This could expose the study to attrition bias due a possibility of non-homogeneity between groups after the participant loss (Akobeng 2008).
Outcome:	The Authors found that pain at rest and when stressed significantly reduced in participants after treatment ($p<0.001$). 80% percent of the participants found excellent or distinct improvements in pain after receiving the intervention which comprised of exercise, manual therapy, correction of body posture, and relaxation techniques. VAS at rest from baseline was 35, pre-treatment was 33, post treatment was 4 and 6 months follow up was 0. VAS at stress from baseline was 72, pre-treatment was 68, post treatment was 23 and 6 months follow up was 11. Impairment in participants also reduced significantly ($p<0.001$) with 20% reporting excellent and 65% reporting distinct improvements in jaw function. Impairment at baseline was 79, pre-test was 76, post-test was 29 and 6 months follow up was 21. There was also no deterioration of symptoms following the interventions. They also found that the therapy significantly improved incisal edge clearance ($p<0.001$) resulting in only 6 patients still having restricted mouth opening versus twelve patients before the intervention. Incisal edge clearance at baseline was 33mm, pre-test was 34mm, post-test was 39mm and 6 month follow up was 39mm. Results remained significant after the 6 months follow up compared to the baseline and pre-test measurements ($p<0.001$).
Discussion:	The aspects of this study that were performed well that would limit the level of bias included the reporting of baseline characteristics and the use of both subjective and objective outcome measurement tools. The factors in this study that introduced bias were the broad inclusion criteria, lack of control on medication use, the design being a single group pre-test post-test with no parallel control group, the lack of randomization or allocation concealment and the lack of assessor blinding. Considering these factors, in addition to the delivery of a programme of care, as opposed to just manual therapy, means that the study not only had a high level of bias, but also no ability to comment on the manual therapy intervention in isolation. Thus, the measurement outcomes cannot be accepted and applied given the high levels of bias and concern in the methodological construct of the study. The applicability of this study's intervention is limited due to the patients being sourced from one location (department of dentistry at the university of Vienna) the broad inclusion and exclusion criteria, the lack of a control to compare to and lack of detail regarding the intervention itself making it difficult for it to be repeated.
Conclusion	Based on the discussion in the block above, limitations in this study created significant bias, which impacts the external validity of the study to a high degree. This seems to concur with the reviewers overall rating of 3/9 using the Newcastle-Ottawa scale indicating a moderate to high level of bias in the internal validity of the study due to lack of specific research controls. Given these impacts of bias, this study was found to have a low level of evidence in support of the combination of exercise, manual therapy, correction of body posture and relaxation techniques to treat symptoms of OA in the TMJ. However, the study cannot contribute to evidence in support of the manual therapy utilized as the study included a treatment programme. Problems that future research would need to address if this study was to be replicated were, having a control group for comparison, randomization of participants, clearly describing each intervention and limiting the number of interventions being investigated.

Table 4.29 Feedback data of article 14: NOS

Author(s):	Qayyum, S. Waqqas, S. Asim, H.					
Year	2017					
Title	Outcomes of Mechanical Traction and Manual Therapy in C5-C6 Cervical Spondylosis for Radicular Pain Relief					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
Selection	1. Is the case definition adequate?	0	0	1	0	66%
	2. Representativeness of the cases	0	0	0	0	100%
	3. Selection of controls	0	0	0	0	100%
	4. Definition of controls	0	0	0	0	100%
Comparability (two point allocation)	5. Comparability of cases and controls on the basis of the design or analysis	0	0	1	0	66%
Exposure	6. Ascertainment of exposure	0	0	0	0	100%
	7. Same method of ascertainment for cases and controls	0	1	0	0	66%
	8. Non-response rate	0	1	0	0	66%
	Total Score	0/9	2/9	2/9	0/9	
		Overall Percentage Agreement:				83%

Table 4.30 Analysis of article 14

Authors	Qayyum, S. Waqqas, S. Asim, H.							
Year	2017							
Title	Outcomes of Mechanical Traction and Manual Therapy in C5-C6 Cervical Spondylosis for Radicular Pain Relief							
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Overall Ranking out of 9	Total Percentage Agreement
1. Numeric pain rating scale (NPRS)	2 measurements. Pre-treatment and post measurement	1 month	50 participants 25 in each group	Not mentioned	Yes The control group was the manipulation group	No	2	83%
Limitations	The recruitment location was the Department of Physiotherapy of the Medical and Dental College in Lahore. So it is assumed that participants were recruited through the Physiotherapy Department or from within the College. Given the reported age (41-60) the participants were older patients that may have previously had manual therapy treatment (and are not naïve) (Akobeng 2008). Since they were only recruited from a single location, generalization to the population may be difficult. (Akobeng 2008; Kendall 2003). The study's criteria included 41-60 year old patients who had C5-C6 cervical spondylosis with radicular symptoms and they needed to have provided consent to participate. Given that study criteria account for confounding variables and promotes homogeneity between the two intervention groups (Assmann et al 2000), this study is open to decreased homogeneity due to the lack of diagnostic criteria (x rays, hospital records or history) and factors like previous surgery or contraindications to treatment (Assmann *et al.* 2000). Additionally, medication use was not accounted or monitored for changes in dose and type of medication. This can influence the outcomes attained in each of the groups (Valdes *et al.* 2017). Randomisation method and concealed allocation were not reported which are important factors to reduce bias in a study (Kendall 2003; Assmann et al 2000). There was no baseline comparison between groups that showed that both groups were equal in important characteristics such as age, gender, occupation type, sedentary or active lifestyle, computer use, co-morbid conditions and stage of degeneration before the interventions took place (Assmann *et al.* 2000; Kendall 2003). For example, participants' occupations should be recorded as certain occupations are associated with an increased risk of OA or may promote progression of the disease. Participants at different stages of degeneration could respond differently which may impact the outcomes as much as the intervention (Dulay *et al.* 2015). The sample size and power of the study were not calculated by the authors to show if the study was adequately powered or not. If underpowered the results could more likely be due to chance or result in type II errors (Kendall 2003; Christley 2010). In terms of treatment, the number of intervention therapist(s) were recorded. If only one therapist was used, a difference in doctor patient dynamics can lead to the doctor emphasizing a clinical outcome for the experimental group over the control group leading to a difference in expectation or impact on the placebo effect (Renjith 2017; Ernst 2007; Kendall 2003). This may have been negated with more than one therapist who were trained in the protocol and applied the protocol similarly. Touch therapy may have also played a role in this study's outcomes if the traction therapy was applied with a machine rather than the practitioners' hands, implying that the manual therapy group would have received more physical contact (Tabatabaee *et al.* 2016). Patient and therapist blinding was not possible given the interventions because the therapy that is applied cannot be replicated in the control group without therapeutic effect. Assessor blinding would assist in negating bias in the study (Renjith 2017). This study however only had one subjective measure, which would have benefitted to a small extent from assessor blinding, and this also predisposes increased risk for patients that are not naïve in presenting outcomes that better reflect their past experience of a known intervention as opposed to the intervention in the research study. Treatment protocols need to be clearly described, including which techniques were used, frequency, intensity, duration of technique per session, number of times the technique was applied per session and load of the technique applied, sequences of techniques and where published the synergistic or antagonistic interaction between treatments. Without this outcomes may not be applicable to clinical practice or future studies as the treatment protocol may be completely different although they may have mentioned using the same technique (Kendall 2003).							

	The authors only used the numeric pain rating scale (NPRS) as an outcome measure. It would have been more beneficial to use an objective form of measurement (Moustgaard *et al.* 2014). This assists in reducing impacts of things like placebo, the Hawthorne effect as well as the input of the participant's past experience with interventions for their condition or knowledge / preconceived ideas around the intervention (Ernst 2007; Akobeng 2008; Sedgwick and Greenwood 2015). The NPRS cannot fully grasp changes in an intervention and should not be used alone for outcome measuring. Blinding of the assessor or the outcome measurer were both not mentioned in this study and are both very important for reducing bias (Moustgaard *et al.* 2014). Finally, outcomes were only measured before and after the intervention, which mens the outcomes are only applicable to the immediate effects following the completion of the intervention with no short term or long term effect measurements.
Outcome:	The authors found that manual traction was significantly more effective in reducing radicular pain in cervical spondylosis than with mobilisation ($p<0.05$). Pain in the manual traction group reduced from a mean of 6.28 pre-treatment to a mean of 1.16 after treatment on the NPRS. Whereas, pain in the mobilisation group reduced from a mean of 6.28 pre-treatment to a mean of 2.68 post treatment on the numeric pain rating scale (NPRS).
Discussion:	Limiting bias in a study is what allows for it to be easily applied on other groups in clinical practice and means that the results were more likely due to the intervention and not due to external factors. The inclusion criteria that the authors mentioned was one such factor that promote homogeneity of groups and reduce bias in the study. factors in this study that may have increase the level of bias are, the lack of an exclusion criteria, the lack of randomization and allocation concealment of participants, not calculating the required sample size for adequate power in a study, not recording baseline characteristics between groups, having only one therapist applying both interventions, not blinding the assessors and using only one form of outcome measurement with that being a subjective form. Based on the limitations the study was found to have a high level of bias which would significantly impact the outcomes of the study. the outcome can be accepted but with a high level of caution because of the high level of bias. However, the study is not applicable in clinical practice mainly because the author did not describe the treatment protocol adequately making it impossible for the same intervention to be repeated in clinical practice or in future research. The authors did not specify the location of where participants were recruited from and the study may have also been underpowered which could have further impacted the generalizability of the study.
Conclusion	Based on the discussion, the limitations had a very large impact on the credibility of the outcomes with the high level of bias found in terms of the external validity. This also agrees with the reviewers overall rating of 0/9 assessing the methodological rigour and internal validity which suggests that there is limited evidence arising out of the study that both mobilisation in a programme and manual traction in a programme significantly reduced pain in participants suffering with cervical spondylosis with cervical traction being the more effective method of treatment. This study however, provides no evidence in support of mobilization alone. The problems that future studies need to consider and address if this study was to be replicated is to have a proper control group for generalization purposes, multiple sources of recruitment, multiple outcome measures including both subjective and objective outcome measures, and randomization of participants.

4.4.3 Case Series

The scale chosen to assess the three case series was the JBI critical appraisal tool for case series. The JBI appraisal tool for case series looks at 10 aspects: the presence of an inclusion criteria, a reliable method of measurement, a valid method of diagnosis, consecutive inclusion of participants, complete inclusion of participants, reporting of demographics and clinical information, clear reporting of results, reporting site demographics and appropriate statistics (Munn *et al.* 2020; Moola *et al.* 2017) responses can be yes, no unclear or not applicable. The scale was scored out of 10 with a yes equalling 1 and any other response equalling a 0.

Table 4.31 List of case series included in this study

Tabulated feedback data	Analysis of articles	Author(s):	Year:	Title:
Table 4.32	Table 4.33	Villafane, J. Silva, G. Fernandez-Carnero, J.	2011	Short-term effects of neurodynamic mobilization in 15 patients with secondary thumb carpometacarpal osteoarthritis
Table 4.34	Table 4.35	Villafane, J. Silva, G. Chiarotto, S.	2012	Effects of passive upper extremity joint mobilization on pain sensitivity and function in participants with secondary carpometacarpal osteoarthritis: a case series
Table 4.36	Table 4.37	Yu, H. Hou, S. Wu, W. He, X.	2011	Upper cervical manipulation combined with mobilization for the treatment of atlantoaxial osteoarthritis: A report of 10 cases.

Table 4.32 Feedback data of article 15: JBI tool for case series

Author(s):	Villafane, J. Silva, G. Fernandez-Carnero, J.					
Year	2011					
Title	Short-term effects of neurodynamic mobilization in 15 patients with secondary thumb carpometacarpal osteoarthritis					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
1	1. Were there clear criteria for inclusion in the case series?	1	1	1	1	100%
2	2. Was the condition measured in a standard, reliable way for all participants included in the case series?	1	1	1	1	100%
3	3. Were valid methods used for identification of the condition for all participants included in the case series?	1	1	1	1	100%
4	4. Did the case series have consecutive inclusion of participants?	0	0	0	0	100%
5	5. Did the case series have complete inclusion of participants?	0	0	0	0	100%
6	6. Was there clear reporting of the demographics of the participants in the study?	1	1	1	1	100%
7	7. Was there clear reporting of clinical information of the participants?	0	1	0	0	66%
8	8. Were the outcomes or follow up results of cases clearly reported?	1	1	1	1	100%
	9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	0	1	1	1	66%
	10. Was statistical analysis appropriate?	1	1	0	1	66%
	Total Score	6/10	8/10	6/10	7/10	
		Overall Percentage Agreement:				90%

Table 4.33 Analysis of article 15

Authors	Villafane, J. Silva, G. Fernandez-Carnero, J.
Year	2011
Title	Short-term effects of neurodynamic mobilization in 15 patients with secondary thumb carpometacarpal osteoarthritis

Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Overall Ranking out of 10	Total Percentage Agreement
1. Pressure pain threshold using a mechanical pressure algometer on the TM joint, tubercle of scaphoid and unciform apophysis of the hamate bone 2. Pinch strength using mechanical pinch gauge for tip pinch and tripod pinch 3. Grip strength using a grip dynamometer	Measured 4 times. Pre-treatment, Post treatment, 1 week following treatment and 2 weeks following treatment	1 month. 2 weeks of treatment and 2 weeks of follow up.	15 participants 13 females and 2 males	Yes	No	No	7/10	90%

Limitations	The patients, in this case series, were aged between 70 to 90 years and recruited from the Department of Physical Therapy (extended care) at the Local Health Unit 3, in Collegno, Italy. They were referred to the Physical Therapy Department by their primary care physician with a diagnosis of stage 3/4 secondary thumb carpometacarpal OA (TCOA) according to the Eaton-Littler-Burton scale (Eaton and Glickel 1987). This implies that the patients are highly specific in their presentation in the study, as they were recruited from a center that is likely to deal with advanced OA presentation, which suggests that the patient presentation is likely to be dissimilar to general OA patient presentation, making the outcomes limited to this specific population. The prospective case series criteria are unlike most case series which are usually designed as retrospective studies (Green and Johnson 2006). Participants were included if they had secondary TCOA in the dominant hand, retained cognitive ability, were ex-factory workers or were house wives. Exclusion criteria included arthritis (unspecified), carpal tunnel syndrome, surgery on the trapeziometacarpal joints or fingers, D'Quervain tenosynovitis, neurological conditions with altered pain sensation and patients with anxiety or depressive disorders. These criteria did not consider medication or other interventions that the patients may have received prior to or during the study intervention period, which may have affected the outcomes (Valdez *et al.* 2017; Kooistra et al 2009; Green and Johnson 2006). Given the recruitment location, the study does not mention whether participants naivety to the study intervention, given that preconceived opinion regarding the intervention (positive or negative) may affect the study outcomes (Akobeng 2008). Additionally baseline characteristics of the patients only included age, sex, Beck Depression Inventory Scale and the State Trait Anxiety Scale, thus homoegenity of the participants is not clear with regards to the pathology under study in addition to descriptive factors that may influence study outcomes. The sample size was made up of 15 participants (13 women and 2 men). The sample size and power of the study were not calculated by the authors to show if the study was adequately powered or not. If underpowered the results could more likely be due to chance or result in type II errors (Kendall 2003; Christley 2010). Outcomes also showed that there were no drop outs or loss to follow up. This study lacked a group to compare results to so the results cannot be attributed solely to the intervention, which implies that the results cannot be generalized to an OA population or to patients that meet the study group criteria (Kooistra et al 2009; Green and Johnson 2006; Carey and Boden 2003). Not having a control group also means that confounding variables such as other interventions being received externally, medication, placebo effect, touch therapy, or even just the natural exacerbation and remission phases of the condition may influence clinical outcomes in one or both groups (Tabatabaee *et al.* 2016; Kooistra et al 2009; Ernst 2007; Green and Johnson 2006; Carey and Boden 2003). Assessor or patient bias may have occurred in this study as all the outcomes were subjective which relied on the patient's judgment. Thus, placebo effects, touch therapy effects, patient naivety, patient blinding (Hartz and Marsh 2003; Kooistra *et al.* 2009), assessor blinding (Hartz and Marsh 2003; Kooistra *et al.* 2009) and assessor influence may have amplified or denigrated measurement outcomes.

	The intervention was described, but detail was limited, thus replication of the study to confirm / refute results is not possible. It is acknowledged that the authors make reference to other articles (Coppieters and Butler 2008; Shacklock 2005) that used the same median nerve mobilisation technique, although it is unclear whether the technique followed was an exact replication of this method. As mentioned earlier, this study only contained objective forms of measurement, therefore misses out on the data regarding, pain levels, patient satisfaction, quality of life and changes in levels of disability which would come from subjective forms of measurement (Kooistra et al 2009). However, this study was strengthened by, its prospective nature reducing the need for memory recall and error in outcomes biased measures (as may be seen in retrospective studies were there is reliance on previously collected data that may be inconsistent) (Hartz and Marsh 2003; Carey and Boden 2003; Kooistra *et al.* 2009). The author had a brief period of follow up for two weeks, mid short term follow up. This may not have been long enough to measure clinical change and /or complications (Kooistra *et al.* 2009). It is also important that no specific clinical practice conclusions should be made using the outcomes due to the lack of a comparison group (due to natural history impact), but rather, only recommendations for research should be made (Kooistra *et al.* 2009).
Outcome:	The authors found that patients suffering with secondary thumb carpometacarpal osteoarthritis who were treated with median nerve mobilisation improved in pressure pain threshold (PPT) on the TM joint and grip strength but pinch strength, PPT on the scaphoid bone and PPT on the hamate bone were insignificant by the end of the follow up (FU) period. PPT in the TM joint pre-test was 3.54 kg/cm2, post-test was 4.38 ($p<0.01$ compared to pre-test), first FU was 4.27 ($p<0.02$ compared to pre-test) and second FU was 4.08 ($p<0.02$ compared to pre-test). PPT on the scaphoid bone pre-test was 5.14, post-test was 5.45 ($p>0.05$), first FU was 5.22 ($p>0.05$) and second follow up was 5.34 ($p>0.05$). Pressure pain threshold of the hamate bone pre-test was 6.12, post-test was 6.92 ($p>0.05$), first FU was 6.96 ($p>0.05$) and second FU was 6.60 ($p>0.05$). Tip and tripod pinch strength pre-test were 2.31 kg and 2.9kg, post-test were 2.57 and 3.28 ($p>0.05$), first FU were 2.48 and 3.18 ($p>0.05$) and second FU was 2.36 and 3.03 ($p>0.05$). Grip strength was 10.77kg pre-test, post-test was 11.55 ($p<0.05$), first FU was 11.73 ($p<0.05$) and second FU was 11.2 ($p<0.05$).
Discussion:	The aspects of the study which would have limited the bias included, being a prospective case series, the use of relatively good study criteria, baseline outcome measurements and a relatively clear and valid definition of the condition. The factors that increased the level of bias in this study included, not having a control/comparison group (along with no randomization or concealed allocation process), no patient blinding, no blinding of the outcome assessor and not accounting for confounding patient characteristic variables such as medication, previous or simultaneous treatment (concurrent to the study), patient naivety and influence of touch therapy. Based on these latter limitations, the study was found to have a high degree of bias impacting the external validity of the study and thus the ability of the study to accurately report the outcomes as being only as a result of the intervention. The study results need to be applied with extreme caution in in clinical practice, but in a research setting it may be possible to repeat this study, as the treatment protocol was only somewhat inadequate and in areas that required more information, references to studies the treatment was replicated from were referenced.
Conclusion	As mentioned in the discussion, the limitation of the study significantly impacted the external validity of the outcomes. The overall rating given by the reviewers was 7/10 which means it was a case series of moderate quality, but in combination with the high degree of bias in external validity the study was found to have a low level of evidence in support of median nerve mobilisation for the treatment of secondary TCOA. Problems that would need to be addressed in future studies are the need for a clinical trial with a comparison group, long term effects also need to be reported and short term effects need to be confirmed. Additionally using this MNMT in addition to other forms of treatment such as routine care may also warrant further investigation.

Table 4.34 Feedback data of article 16: JBI tool for case series

Author(s):	Villafane, J. Silva, G. Chiarotto, S.					
Year	2012					
Title	Effects of passive upper extremity joint mobilization on pain sensitivity and function in participants with secondary carpometacarpal osteoarthritis: a case series					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
1	1. Were there clear criteria for inclusion in the case series?	1	1	1	1	100%
2	2. Was the condition measured in a standard, reliable way for all participants included in the case series?	1	1	1	1	100%
3	3. Were valid methods used for identification of the condition for all participants included in the case series?	1	1	1	1	100%
4	4. Did the case series have consecutive inclusion of participants?	0	1	0	0	66%
5	5. Did the case series have complete inclusion of participants?	1	1	0	1	66%
6	6. Was there clear reporting of the demographics of the participants in the study?	1	1	1	1	100%
7	7. Was there clear reporting of clinical information of the participants?	0	1	0	0	66%
8	8. Were the outcomes or follow up results of cases clearly reported?	1	1	1	1	100%
	9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	0	1	1	1	66%
	10. Was statistical analysis appropriate?	1	1	1	1	100%
	Total Score	7/10	10/10	7/10	8/10	
		Overall Percentage Agreement:				86%

Table 4.35 Analysis of article 16

Authors	Villafane, J. Silva, G. Chiarotto, S.							
Year	2012							
Title	Effects of passive upper extremity joint mobilization on pain sensitivity and function in participants with secondary carpometacarpal osteoarthritis: a case series							
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Overall Ranking out of 13	Total Percentage Agreement
1. Visual analog scale (VAS) measuring pain severity. 2. Pain pressure threshold using mechanical pressure algometer. 3. pinch strength using a mechanical pinch gauge.	Outcomes measured four times. Pre-treatment, Post treatment, First follow up 1 week after treatment and second follow up 2 weeks after treatment.	1 month	15 participants. 13 females and 2 males.	No	No	No	8/10	86%
Limitations	As with the previous case series, these participants of this study were recruited from the same Department of Physical Therapy, indicating that the study is subject to the same limitations of a specific population type that may not allow for the study results to be extrapolated to all OA patients seen in general practice (Carey and Boden 2003). The study included, a total of 2 men and 13 women, aged between 70 to 90 years and who presented with secondary carpometacarpal (CMC) OA. This case series was a prospective study, with study criteria that included participants if they had preserved mental capacity, were ex factory workers or housewives (or individuals who methodically used their dominant hand often) and were diagnosed with stage 3/4 CMC OA according to the Eaton-Littler-Burton classification (Eaton and Glickel 1987). Patients were excluded if they had arthritis (unspecified), carpal tunnel syndrome, surgery on the CMC joint, D'Quervain tenosynovitis, neurological conditions with altered pain sensation and specific outcomes on the Beck Depression Inventory and the State Trait Anxiety Inventory questionnaires. However, the authors had limited control for medication use (prior or during the study), no limitations on other interventions (received prior to or during the study period), or patient naivety (given the recruitment from a specialised center) all of which many have impacted the results (Valdez *et al.* 2017; Akobeng 2008; Hartz and Marsh 2003). The base line measurements of the study included age, sex, BDI and STAI. These are all important factors so that future research has reference to a well described population and condition for it to be repeated easily (Carey and Boden 2003). Thus, this study has some flaws in the description and control of patient characteristics that may have influenced the outcome, particularly since there is no control group that allows for these factors to be compared to and controlled for and thus negating their impact on the ability of the study to measure the actual clinical effect of the intervention. This study had a small sample size, meaning the results cannot be solely attributed to the intervention, given the influence of the patient characteristics above and the possibility that the outcomes may not be more than chance itself (small samples predispose to type II error in reporting outcomes) (Kooistra *et al.* 2009; Carey and Boden 2003). This is further compounded by a lack of randomization of participants or concealed allocation due to the lack of a comparison group which significantly increases the level of allocation, researcher and patient influence bias' in the study (Kooistra et al 2009; Green and Johnson 2006; Carey and Boden 2003). Patient influence bias includes whether outcomes are due to the intervention, or due to other factors such as patient characteristics, external interventions, medication, placebo effect, touch therapy or just the natural history of the condition (Tabatabaee *et al.* 2016; Ernst 2007; Green and Johnson 2006; Carey and Boden 2003). One element that could have been managed in a case series, is blinding the outcome assessor to prevent assessor/information bias (Hartz and Marsh 2003). This was not mentioned (Kooistra *et al.* 2009; Hartz and Marsh 2003). The authors' credit, it was noted that no participants dropped out of the study during all phases of the study. In terms of the intervention protocol, the treatment technique required more clarification than was provided for it to be replicated (Kooistra *et al.* 2009; Green and Johnson 2006). Adequate detail was given on the patient position and doctor position, however the mobilisation movement involving the elbow, wrist and hand							

	required more detail for it to be repeated with ease in future studies. A diagram or a picture of what the manoeuvre looked like would have made replication easier. Outcomes measures chosen were the VAS, pressure pain threshold and pinch strength which were described and referenced to be valid and reliable outcome measures (Kooistra *et al.* 2009). This includes both subjective and objective measures which is necessary to maximize gained data (Kooistra *et al.* 2009). The authors considered the period of follow up that they used in this study was mid short term in length and were aware that they cannot discuss the long term effects of their study. Future studies should look to have a long term of follow up. The authors also mentioned that no complications or adverse effects occurred following the intervention or during the follow up period which is important for future studies to know (Agha *et al.* 2016; Gagnier *et al.* 2014). Finally, the authors mentioned the limitations in the management of patients in their study clearly as well as any other limitations in the study process which can help inform future studies and prevent the same mistakes form happening (Agha *et al.* 2016; Gagnier *et al.* 2014)
Outcome:	The authors found that passive joint mobilisation to the dominant arm, wrist and hand in Secondary carpometacarpal osteoarthritis sufferers reduced in pain, increased in pain pressure threshold and increased in pinch strength. VAS (mm) at CMC joint recorded at pre-test was 64.53, post-test was 59.63 ($p>0.05$ pre-test/post-test), First FU was 45.27 ($p<0.05$ pre-test/ first FU) and second FU was 55.97 ($p>0.05$ pre-test/second FU). PPT (kg/cm²) at CMC joint at pre-test was 4.04, post-test was 4.24 ($p>0.05$), first FU was 4.58 ($p>0.05$), and second FU was 4.40 ($p>0.05$). PPT at scaphoid bone at pre-test was 5.33, post-test was 5.55 ($p>0.05$), first FU was 5.51 ($p>0.05$) and second FU was 5.72 ($p>0.05$). PPT at hamate bone at pre-test was 6.02, post-test was 6.69 ($p>0.05$), first FU was 7.18 ($p<0.05$) and second FU was 6.76 ($p>0.05$). Tip pinch strength (kg) at pre-test was 1.99, post-test was 2.15 ($p>0.05$), first FU was 2.13 ($p>0.05$) and second FU was 2.15 ($p>0.05$). Tripod pinch strength (kg) at pre-test was 2.39, post-test was 2.82 ($p=0.05$), first FU was 2.67 ($p>0.05$) and second FU was 2.71 ($p>0.05$).
Discussion:	This was a well performed case series, however this study still falls prey to inclusion criteria that are not very limiting and do not control for confounding variables thus not allowing for a well described population and a well-defined clinical condition; the lack of a control group which may have controlled for some confounding variables; the lack of randomisation or allocation concealment as well as and no assessor or patient blinding. These limitations along with a small study sample size indicate that there is a high risk for a type II error and / or drawing conclusions in respect of the interventions that may not be better than chance or natural history alone. Thus, the level of bias and its impact on external validity is high. This limits the ability of the conclusions to be used in clinical practice. But, due to the positive clinical outcomes, it can be used to inform future studies that look to replicate this intervention in the form of a larger clinical trial.
Conclusion	Based on the discussion, the limitations are seen to highly bias the outcomes and thus impact on the external validity. The overall rating the reviewers gave the study was 8/10 using the JBI critical appraisal tool for case series indicating that the case series was well written and performed. Therefore although the study was well reported and conformed to the publication requirements in terms of a case study structure, the outcomes are potentially highly influenced by the impact of bias on the external validity of the study. Therefore at best this study provides limited to no evidence in support of the intervention utilized in this study. Future research is required to confirm or refute the study's findings, principally through the use of a RCT design.

Table 4.36 Feedback data of article 17: JBI tool for case series

Author(s):	Yu, H. Hou, S. Wu, W. He, X.					
Year	2011					
Title	Upper cervical manipulation combined with mobilization for the treatment of atlantoaxial osteoarthritis: A report of 10 cases.					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
1	1. Were there clear criteria for inclusion in the case series?	0	0	1	0	66%
2	2. Was the condition measured in a standard, reliable way for all participants included in the case series?	1	1	1	1	100%
3	3. Were valid methods used for identification of the condition for all participants included in the case series?	0	0	1	0	66%
4	4. Did the case series have consecutive inclusion of participants?	0	0	0	0	100%
5	5. Did the case series have complete inclusion of participants?	0	0	0	0	100%
6	6. Was there clear reporting of the demographics of the participants in the study?	1	1	1	1	100%
7	7. Was there clear reporting of clinical information of the participants?	1	1	0	1	66%
8	8. Were the outcomes or follow up results of cases clearly reported?	1	1	1	1	100%
	9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	1	1	0	1	66%
	10. Was statistical analysis appropriate?	0	1	0	0	66%
	Total Score	5/10	6/10	5/10	5/10	
		Overall Percentage Agreement:				83%

Table 4.37 Analysis of article 17

Authors	Yu, H. Hou, S. Wu, W. He, X.							
Year	2011							
Title	Upper cervical manipulation combined with mobilization for the treatment of atlantoaxial osteoarthritis: A report of 10 cases.							
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Overall Ranking out of 10	Total Percentage agreement
1. Numeric Pain scale: to measure neck pain 2. Rotation of C1-C2 3. Radiographic examination of atlantoaxial facet joint space 4. Categorical scale of excellent, good, fair or poor.	Pre-test and post-test	Unknown	10	Not applicable	No	No	5/10	83%
Limitations	This case series had several limitations. The first being the lack of clarity as to where the study took place – in the USA or China. What is apparent is that the study took place at either the Department of Orthopedics from a general military hospital in Beijing, China or at the Palmer College of Chiropractic. These two location possibilities have a significant impact on the recruitment of participants into the study in terms of demographics and patient characteristics, which means that the study has a limited context, with the exception of the reported patient characteristics. The inclusion of patient data, was limited to patients who had neck pain, atlantoaxial osteoarthritis and who had not received treatment (upper cervical manipulation combined with an auxiliary spine adjuster) five years prior to the beginning of the study. This broad inclusion does not describe the study population well as it did not include a definition of the condition being treated, criteria for diagnosing the condition and a description of the population (namely, age, gender, occupation, medication use, comorbid conditions) (Care and Boden 2003). The sample consisted of five females and five males suffering with neck pain and atlantoaxial OA, with an average age of 50 years. Four patients had no obvious trauma and six patients had a history of neck or head trauma with radiographic evidence of atlantoaxial OA. It is reported that the patients complained of unilateral neck pain with rotation, had limited range of motion between C1 and C2, there were no signs of neurological pathology and a clear Doppler ultrasound to exclude vertebral artery conditions. The characteristics that the authors failed to mention was the socioeconomic status of the patients, the severity of the conditions in the patients, duration the patients had the condition for and whether they were naïve to the intervention before starting (Carey and Boden 2003). Since this study was a retrospective case series, it had no control group, randomization, concealed allocation, baseline comparisons and the calculation of the study power was not reportedly performed. With the lack of a comparison or control group, it is unclear as to whether the outcomes are due to the intervention or due to another cause such as the natural history, confounding patient characteristics and or patient influence (viz patient naivety) (Kooistra *et al.* 2009; Green and Johnson 2006). Therefore it is possible that the clinical outcomes may not be more than chance and no conclusions of cause and effect can be drawn (Kooistra et al 2009; Green and Johnson 2006; Carey and Boden 2003). These assertions are compounded by the study being a retrospective investigation, where rigorously developed protocols before the commencement of the study cannot be verified. In addition retrospective studies also suffer from incomplete data collection as well as incomplete patient follow up. Usually data also tends to not be measured in a standardized manner using suitable and valid outcome measures rather the measures that were used in routine care (which often happens in a case series). All of these factors increase bias in the study and impact its outcomes (Kooistra *et al.* 2009; Green and Johnson 2006; Hartz and Marsh 2003). In addition to the above, the choice of inclusion of participants in this study may have been defined by those that complied with the treatment protocol and measurements, therefore there is no accounting for the follow ups lost to worsening of the condition, seeking alternative treatment or other limiting factors (e.g. patient moved away). Therefore it is likely that the data reports on patients that were compliant and thus the outcome may report better than it may be in clinical practice (Kooistra *et al.* 2009).							

	The apparent flaws in data collection include the lack of a blinded assessor, or in the judgment of the changes in atlantoaxial joint space as the therapist may have assessed it favourably as well (Hartz and Marsh 2003). Since this is a case series, the length of follow up also varied considerably from the shortest follow up period on a patient being 10 months to the longest being seven years for only 10 participants, so comparability is an issue. There were also very few participants with multiple uncontrolled patient characteristics that were included in this study limiting the generalizability of the results. The study should have focused on one specific group of patients to allow for more consistency in the outcomes, homogeneity between participants and prevent confounding variables from causing bias (viz reducing the ability to ascribe the outcomes to the intervention) (Kooistra et al 2009) The intervention was not described adequately for it to be repeated. It was reported that high velocity low amplitude (HVLA) thrusts were applied with a mechanical spinal adjuster in addition to some participants requiring massage to reduce muscle tension before manipulation could be performed. However, the number of sessions, the treatment protocol during the session, the number of manipulative procedures performed on the patients, the locations that were manipulated and the exact method of how the manipulation was performed were not mentioned. This makes this case report very difficult to replicate (Kooistra *et al.* 2009; Green and Johnson 2006) The outcome measures were based on routine care measures, because a retrospective case series cannot dictate the measurement tool(s) chosen (Hartz and Marsh 2003). There was a balance of subjective and objective measurement tools, however, the validity and reliability of the measurement tools were omitted (Kooistra *et al.* 2009; Hartz and Marsh 2003). Measurement tools such as those that measure patient satisfaction, quality of life and disability levels can help maximise on the data gained such as the Oswestry Disability Index (ODI) (Igatpurikar 2013; Kooistra *et al.* 2009, but these were excluded. The mean changes pre- and post-treatment using the NPS and rotation of C1-C2 were reported, but the timing of the post-treatment measurement was unreported (seemed to take place at different time periods for different patients which limits actual comparability, impacting conclusions (Hartz and Marsh 2003). Outcome assessors were also not blinded introducing researcher bias (Kooistra *et al.* 2009).
Outcome:	The authors reported that Chiropractic manipulation using HVLA thrusts to the cervical spine with a mechanical spinal adjuster led to improved signs and symptoms in atlantoaxial arthritis sufferers. Improvements in the NPS from a mean average of 8.6/10 to 2.6/10 and an improvement in mean rotation of C1-C2 from 28 degrees to 52 degrees. Relief of pain following the intervention were categorized as excellent, good, fair, or poor. Four participants reported “excellent”, three reported “good”, one reported “Fair” and two reported “poor”. The radiological outcomes were reported based on atlantoaxial joint space before and after treatment and categorized as none, partial or full radiological improvement. One patient had full improvement, eight with partial improvement and one patient with none. No p values were given on any of the outcomes.
Discussion:	The authors noted that the outcomes suggested that upper cervical manipulation with mechanical spinal adjuster can improve signs and symptoms of atlantoaxial osteoarthritis due to either degeneration or trauma. This conclusion cannot be stated so categorically in a case series as the study lacked a comparison group, had multiple patient characteristics that were uncontrolled and did not have a clear intervention and measurement strategy that was predefined. All these factors place the outcomes on a no better than chance or natural history footing (Kooistra et al 2009; Green and Johnson 2006; Carey and Boden 2003). This is further confounded by a very sample sample size that may be skewed in favour of the outcome given that retrospective studies cannot control for patients that would have fallen out of the study for worsening of the condition. This study would be difficult to replicate as there was no intervention protocol noted. Ideally, future studies would repeat this as a RCT.
Conclusion	Based on the discussion, the limitations significantly impacted the external validity of the outcomes as a result of the high level of bias. This prevents its use in clinical practice without significant caution. The overall rating of the reviewers using the JBI critical appraisal tool for case series was 5/10 indicating that it was a case series of moderate quality which was mentioned in the limitations. Therefore this study presents with no evidence in favour of mobilisation alone as mobilisation was used as part of a programme. Future studies that would like to replicate this study would need to address it in an RCT that can determine the applicability of this approach in clinical practice.

4.4.4 Case Reports

The Scale chosen to assess the three case reports was the JBI critical appraisal tool for case reports (Moola *et al.* 2017). The Appraisal tool looks at 8 characteristics in a study: the description of patient demographics, a clear patient history, clear presentation of condition, clear description of assessments diagnostics methods, clear intervention protocol, clear post-intervention condition, described adverse events, and mentioning take away lessons. Responses to the questions can be yes, no, unclear or not applicable. A yes awards the question one point where as any other response give it a 0 allowing for a total of 8 point per article.

Table 4.38 list of case reports included in this study

Tabulated feedback data	Analysis of articles	Author(s):	Year	Title:
Table 4.39	Table 4.40	Crowell, M. S. Tragord, B. S.	2015	Orthopaedic Manual Physical Therapy for Shoulder Pain and Impaired Movement in a Patient with Glenohumeral Joint Osteoarthritis: A Case Report
Table 4.41	Table 4.42	Sokunbi, O.G.	2015	Manual Therapy and Acupuncture in the Treatment of Patient with Cervical Spondylosis with Radicular Pain- Case Report
Table 4.43	Table 4.44	Villafane, J. Langford, D. Alguacil-Diego, I. Fernandez-Carnero, J.	2013	Management of trapeziometacarpal osteoarthritis pain and dysfunction using mobilization with movement technique in combination with kinesiology tape: a case report

Table 4.39 Feedback data of article 18: JBI tool for case reports

Author(s):	Crowell, M. S. Tragord, B. S.					
Year	2015					
Title	Orthopaedic Manual Physical Therapy for Shoulder Pain and Impaired Movement in a Patient with Glenohumeral Joint Osteoarthritis: A Case Report					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
1	1. Were patient's demographic characteristics clearly described?	1	1	1	1	100%
2		0	1	1	1	66%
3	3. Was the current clinical condition of the patient on presentation clearly described?	1	1	1	1	100%
4	4. Were diagnostic tests or assessment methods and the results clearly described?	1	1	1	1	100%
5	5. Was the intervention(s) or treatment procedure(s) clearly described?	1	1	1	1	100%
6	6. Was the post-intervention clinical condition clearly described?	1	1	1	1	100%
7	7. Were adverse events (harms) or unanticipated events identified and described?	0	0	0	0	100%
8	8. Does the case report provide takeaway lessons?	0	1	1	1	66%
	Total Score	5/8	7/8	7/8	7/8	
		Overall Percentage Agreement:				92%

Table 4.40 Analysis of article 18

Authors	Crowell, M. S. Tragord, B. S.							
Year	2015							
Title	Orthopaedic Manual Physical Therapy for Shoulder Pain and Impaired Movement in a Patient with Glenohumeral Joint Osteoarthritis: A Case Report							
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Overall Ranking out of 8	Total Percentage Agreement
1. Shoulder pain and disability index (%) 2. patient specific functional scale (0-10)	6 times At baseline, 4 weeks (completion of 5 sessions), 8 weeks (after 6th final session), 6 months, 9 months, 12 months	1 year	1	no	no	no	7/8	92%
Limitations	The case was described adequately which included the patient's age, dominant hand, race, occupation, duration of condition as well as stage of condition. Given that this was a case report of a single 38 year old male patient, the exact location of where he was recruited from is not evident. Selection bias can play a role in this study as the practitioner may have chosen the patient, the measurement frequency and the outcome measures that were most suitable to report (Kooistra *et al.* 2009). This data can therefore not be generalized to any population (Kooistra *et al.* 2009; Green and Johnson 2006; Carey and Boden 2003; Hartz and Marsh 2003). This is because case reports lack a properly sized sample and a comparison group so the intervention cannot be isolated as the sole reason for patient improvement, given the patients specific contextual characteristics (Kooistra et al 2009; Green and Johnson 2006; Carey and Boden 2003). This is further compounded as it is unclear whether the study was done prospectively or retrospectively (Green and Johnson 2006). Studies performed such as this one in uncontrolled environments where patients can introduce confounding variables such as medication or other interventions which the clinician cannot prevent can lead to false positive or negatives, which can seriously affect the outcomes (Kooistra et al 2009; Green and Johnson 2006). The above discussion is compounded by the lack of inclusion criteria, but countered by a defined outline of the condition and criteria for diagnosis, where the patient was diagnosed with severe glenohumeral joint OA according to the Samilson-Prieto and Walch classification systems (Crowell and Traggord 2015; Carey and Boden 2003). Unanticipated or adverse events that occurred during or following the study were not mentioned in this study, which provides for an inability to contextualise the outcomes (Agha *et al.* 2016; Gagnier *et al.* 2014). This study followed up on the patient for one year with four booster sessions given at nine months following the first interventions compounding the actual effects achieved at the two intervention periods (Kooistra et al 2009). Finally, the author did not mention if there were any limitations in the management of this patient's case or in their study process that could inform future research and prevent similar mistakes (Agha *et al.* 2016; Gagnier *et al.* 2014). This latter may also have been influenced by the placebo effect, researcher bias and therapist bias (Hartz and Marsh 2003) as well as natural history (Green and Johnson 2006; Carey and Boden 2003); but without a control group, these affects cannot be accounted for. The description provided by the authors on the intervention that they used on the patient was adequately described for it to be replicated in future research. In places where further information was needed regarding the intervention, studies were referenced that contained the information (Kooistra *et al.* 2009; Green and Johnson 2006). Experimental studies should contain both objective and subjective measures to maximize on the gained data, with which this study complied. But the author did not report or compare the pre- and post-test values of these objective measures in the outcome section, only focusing on the subjective measure (SPADI) values that changed following intervention completion (Kooistra *et al.* 2009). The validity and reliability of the SPADI was noted as it was the primary form of outcome measurement (Kooistra et al 2009; Carey and Boden 2003). A blinded outcome assessor may have assisted to improve the study, however this was not mentioned in this study (Kooistra 2009).							
Outcome:	The authors found that using manual physical therapy along with exercise in a patient with glenohumeral joint osteoarthritis was very beneficial. Shoulder pain and disability index (SPADI) made up of a pain subscale and function subscale at baseline was 43%, 4 weeks was 17%, 8 weeks was 4%, 6 months was 9 %, 9 months was 8% and 12 months was 13%. Patient specific functional scale (PSFS) with subscales of working out, bow hunting, sleeping and scratching back at Baseline was 3.0, 4 weeks was 7.3, 8 weeks was 9.0, 6 months was 9.0, 9 months was 9.0 and 12 months was 8.0. Author also reported that after 8 weeks of treatment, patient showed symmetrical active and passive shoulder movements with equal muscle strength. No p values were given.							

Discussion:	The results gained from this study are questionable for glenohumeral joint osteoarthritis sufferers. In the context of a case report all it can be used for is to inform further research. Although this case report was performed well, having a clear description of the patient case, examination, method of diagnosis and a clear description of the treatment; the study design added high levels of bias impacting on the outcomes (namely, the lack of a large enough sample, lack of a control, lack of randomization (research bias), and the lack of assessor blinding). The intervention was also a part of a programme making it impossible to separate the effects of the queried intervention, thus the conclusions cannot be accepted and it cannot be implemented in clinical practice, unless the patient meets all patient characteristics as outlined in this report and then too with caution.
Conclusion	Based on the limitations of the study which are significant given the case reporting structure, the external validity was highly compromised even though the reviewers provided the study an overall rating of 7/8 using the JBI critical appraisal tool for case reports. In view of this and in addition to mobilisation being a part of a programme the case report provides no evidence in support of mobilisation alone Future studies look to replicate this study should look at performing a randomized controlled trail which can then be used as an evidence base for information on this method of treatment.

Table 4.41 Feedback data of article 19: JBI tool for case reports

Author(s):	Sokunbi, O.G.					
Year	2015					
Title	Manual Therapy and Acupuncture in the Treatment of Patient with Cervical Spondylosis with Radicular Pain- Case Report					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
1	1. Were patient's demographic characteristics clearly described?	0	0	1	0	66%
2	2. Was the patient's history clearly described and presented as a timeline?	0	1	0	0	66%
3	3. Was the current clinical condition of the patient on presentation clearly described?	0	1	1	1	66%
4	4. Were diagnostic tests or assessment methods and the results clearly described?	1	1	0	1	66%
5	5. Was the intervention(s) or treatment procedure(s) clearly described?	0	1	1	1	66%
6	6. Was the post-intervention clinical condition clearly described?	0	1	1	1	66%
7	7. Were adverse events (harms) or unanticipated events identified and described?	1	1	0	1	66%
8	8. Does the case report provide takeaway lessons?	0	1	1	1	66%
	Total Score	2/8	7/8	5/8	6 /8	
		Overall Percentage Agreement:				66%

Table 4.42 Analysis of article 19

Authors	Sokunbi, O.G.							
Year	2015							
Title	Manual Therapy and Acupuncture in the Treatment of Patient with Cervical Spondylosis with Radicular Pain- Case Report							
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Overall Ranking out of 8	Total Percentage Agreement
1. Numerical pain rating scale 2. Neck pain and disability scale	7 times. Pre-test, after first week of treatment, 2nd week, 3rd week, 4th week, 5th week and 6th week (at completion of treatment)	6 weeks	1	no	no	no	6/8	66%
Limitations	The study was done through the Department of Physiotherapy at the University of Maidguri in Nigeria. Similar to the previous study, this study is a case report. Thus the design lacks a large enough sample of participants and does not contain a group for to be compared to. This limits external validity impacting on the generalisability of the outcomes (Kooistra et al 2009; Green and Johnson 2006; Carey and Boden 2003). Therefore, only a hypothesis can be made about what appears to be a relationship between the intervention outcome and the patient's condition. The authors did not mention If this study was performed prospectively or retrospectively, which is important to mention as retrospective studies rely on previously gathered information which in most cases tends to be incomplete and can lead to deficiencies in the report (Green and Johnson 2006). Clear patient characteristics, a definition of the condition, the criteria used to diagnose the spondylosis, as well as the stage and duration of the illness are important (Carey and Boden 2003). The author defined the condition being investigated, the age and gender of the patient. However, it was not clear duration of symptoms, it was reported that onset of symptoms was about six months prior to referral to for physiotherapy treatment (but not whether this presentation was for the current case study). Additionally, the diagnostic criteria were not provided so it is unclear which future patients may benefit from a similar intervention (Kooistra 2009: Carey and Boden 2003; Agha *et al.* 2016; Gagnier *et al.* 2014). In terms of patient characteristics, further details omitted were the socioeconomic status, ethnicity, occupation, and prior trauma without which identification of appropriate patients for similar care is limited (Carey and Boden 2003). In terms of the intervention, it was not reported whether the patient was naïve to the intervention (six month history suggests exposure to treatments both within and outside of the study) before entering the study. This impacts on the subjective only approach in this study, as patient perception is known to influence this (Akobeng 2008). Selection bias, lack of randomisation, concealed allocation, researcher bias and outcomes assessor bias (Hartz and Marsh 2003) further complicate with use of only subjective measures in addition to the sample size of one. This is further complicated by the placebo effect and the Hawthore effect (Sedgwick and Greenwood 2015; Ernst 2007) as well as the natural history of the condition (Kooistra et al 2009; Green and Johnson 2006; Carey and Boden 2003). Confounding variables which were not considered in the inclusion of the patient as well as being in an uncontrolled environment further impact the outcomes (Hartz and Marsh 2003). The only noted variable that was controlled was medication (which was stopped ahead of the study). In terms of the intervention, the patient that was reported to have had received treatment for six weeks and was available for that amount of time. Therefore, this implies that patients cannot at best stop treatment before this time to get similar results (Kooistra et al 2009). To the credit of the authors, the acupuncture techniques were described in the article and referenced to their sources adequately. The manual therapy technique was described well but omitted were how many times the therapist applied the manual thrust in a single session and the exercises that the participant was given. This limits replication of the study (Kooistra et al 2009; Green and Johnson 2003). A reliable method of measuring outcomes objectively should have also been used such as cervical mobility, because a study should contain a balance of both objective and subjective measures (Kooistra *et al.* 2009). The study contained two subjective forms of measurement that were referenced to be both valid and reliable which is necessary for outcomes to be repeatable (Kooistra *et al.* 2009; Carey and Boden 2003). Blinding of outcome assessors is important and was not reported (Kooistra *et al.* 2009). Furthermore, short term and long term follow up after the intervention was not performed and are both important in assessing for any change, complications, or how long it takes for the							

	treatment to wear off which can help inform future research (Kooistra *et al.* 2009). The author mentioned the limitations in the study and in the patient's management which could inform future research and prevent similar mistakes (Agha *et al.* 2016; Gagnier *et al.* 2014). Finally, the author did not account for any unanticipated or adverse events which should be mentioned I n a case report (Gagnier *et al.* 2014).
Outcome:	The author found that manual therapy, exercise and acupuncture combined, successfully reduced pain levels and improved function in a patient suffering with cervical spondylosis with radicular pain. Numeric pain rating scale (NPRS) reduced 8/10 before treatment to 0/10 at the completion of treatment. There were no calculated p values in this study While the author suggested in his conclusion that spinal manipulation , exercise and acupuncture can be cautiously considered for treating cervical spondylosis sufferers with radicular pain, no absolute conclusions should be stated because the lack of a comparison group prevent any hypothesis from being tested (Kooistra *et al.* 2009)
Discussion:	The main concern in this study is the limitations have significantly impacted the outcomes through a high level of bias. This study is designed as a case report, having only one participant and no comparison group, the significant noted limitation which draws attention away from the ability to directly attribute the outcomes to the intervention. The study was also performed as a programme and not as a single intervention alone meaning the outcome of mobilisation cannot be separated from the results. Given this, the study was found to have a high level of bias, meaning it can only be accepted for replication in future, but cannot be accepted as a source of evidence to implement in clinical practice. As for its ability to be replicated in future research, the manual therapy and acupuncture protocols were described adequately, but the exercise programme was not, so if attempted to be replicated, results may differ because the exercise therapy would not be exactly the same, limiting the replicability,
Conclusion	Based on the limitations of the study which are significant given the case reporting structure, the external validity was highly compromised even though the reviewers provided the study an overall rating of 6/8 using the JBI critical appraisal tool for case reports. In view of this, and since intervention was provided as part of a programme the case report provides no evidence for the intervention. Future studies looking to replicate this study should look at performing a randomized controlled trail which can then be used as an evidence base for information on this method of treatment. Additionally, A single intervention should be administered to the group for results to be relevant.

Table 4.43 Feedback data of article 20: JBI tool for case reports

Author(s):	Villafane, J. Langford, D. Alguacil-Diego, I. Fernandez-Carnero, J.					
Year	2013					
Title	Management of trapeziometacarpal osteoarthritis pain and dysfunction using mobilization with movement technique in combination with kinesiology tape: a case report					
Criteria:		Reviewer 1	Reviewer 2	Reviewer 3	Majority	Percentage agreement
1	1. Were patient's demographic characteristics clearly described?	1	1	1	1	100%
2	2. Was the patient's history clearly described and presented as a timeline?	0	1	1	1	66%
3	3. Was the current clinical condition of the patient on presentation clearly described?	1	1	1	1	100%
4	4. Were diagnostic tests or assessment methods and the results clearly described?	1	1	1	1	100%
5	5. Was the intervention(s) or treatment procedure(s) clearly described?	1	1	1	1	100%
6	6. Was the post-intervention clinical condition clearly described?	0	1	1	1	66%
7	7. Were adverse events (harms) or unanticipated events identified and described?	0	0	1	0	66%
8	8. Does the case report provide takeaway lessons?	0	1	1	1	66%
	Total Score	4 /8	7/8	8/8	7/8	
		Overall Percentage Agreement:				83%

Table 4.44 Analysis of article 20

Authors	Villafane, J. Langford, D. Alguacil-Diego, I. Fernandez-Carnero, J.							
Year	2013							
Title	Management of trapeziometacarpal osteoarthritis pain and dysfunction using mobilization with movement technique in combination with kinesiology tape: a case report							
Form of measurement	Frequency of measurement	Duration of study	Number of participants	Assessors Blinded	Control used	Randomization of participants	Overall Ranking out of 8	Total Percentage Agreement
1. Numeric Pain scale 2. Hospital anxiety and depression scale (HADS) 3. Goniometric evaluation of the thumb for range of motion (ROM) 3. Pressure pain threshold (PPT) using a mechanical pressure algometer 3. Tip pinch strength using a mechanical pinch gauge	3 times. Pre-test, Post-test and 2 months follow up after completion of intervention	4 months	1	no	no	no	7/8	83%
Limitations	This study took place at a Physiotherapy Clinic. The patient was well described including her age, gender, occupation severity of condition, duration of condition, medication use, previous medical history as well as the criteria used to diagnose her condition which are needed so the reader and researchers looking to replicate the study understand the study population as well as who the treatment would be effective for (Agha et al 2016; Gagnier *et al.* 2014; Kooistra et al 2009; Carey and Boden 2003; Valdez *et al.* 2017; Hartz and Marsh 2003). The study was designed as a case report which means that the results cannot be generalized back to the population, nor can it be said to exclusively provide an environment that allows for measurement of the intervention (Villafane *et al.* 2013; Kooistra *et al.* 2009; Carey and Boden 2003). This assertion is based on the fact that the outcomes may be due to the natural history, the placebo effect, the Hawthorne effect, patient naivety, selection bias (Sedgwick and Greenwood 2015; Kooistra et al 2009), lack of control of patient characteristics or other influencers that impact the ability to measure the intervention effect only (Kooistra *et al.* 2009; Green and Johnson 2006; Ernst 2007; Carey and Boden 2003). Additionally, the authors also used more than one intervention on the patient which makes it impossible to identify which intervention was most effective (Villafane *et al.* 2013). The most important limitation is in the design of study, given that it is a case report, it only contains one participant and does not have a control or comparison group meaning no cause and effect can be concluded from the outcomes and the outcomes cannot be generalized back to a population (Kooistra *et al.* 2009; Green and Johnson 2006; Carey and Boden 2003). The authors described more than one intervention on the patient which makes it impossible to identify which intervention was most effective (Villafane *et al.* 2013). As for the description of the intervention, both the mobilisation with movement (MWM) and kinesiology taping were very briefly described. The MWM technique was not adequately described in the article, instead, another article was referenced as the source of the technique. The technique should have been elaborated on more especially on the technique of manual gliding pressure which is what the practitioner needed to perform on the patient before the patient could perform thumb motions. The kinesiology taping also required more detail regarding the placement of the tape as well as the secondary corrective tape that was placed over the snuff box and parallel to the tendons. The lack of some details may make it difficult for this intervention to be replicated in future studies (Green and Johnson 2006). The study may have been further affected through information bias. This can occur in studies where objective measures are used which require the judgment of the researcher. If the researcher favours that intervention, they may record outcomes favourably or exaggerate to produce a better outcome (Kooistra et al 2009; Hartz and Marsh 2003). This bias can be avoided using a blinded outcome assessor which was not mentioned in this study (Kooistra *et al.* 2009). Both objective and subjective outcomes are recommended to be used to maximize the data that can be gained in a study. This study used 3 objective measures and 2 subjective measures which is a good balance of objective and subjective measures (Kooistra *et al.* 2009). However an important measure that should have been included is one that measures patient satisfaction, relief of symptoms and quality of life such as the Oswestry disability index (ODI) scale which significantly add to the data (Kooistra *et al.* 2009; Igatpurikar 2013). The total period of follow up after the completion of the intervention was 2 months. The author did not indicate whether this was considered short term or an intermediate period of follow up. However an adequate period of follow up is necessary to assess for changes, complications and duration of effect of the intervention (Kooistra et al 2009). The							

	author also did not make any conclusion using the outcome except that the outcomes justify further clinical trials using this technique due to the improvements that were found which is correct in the case of case reports and series (Kooistra *et al.* 2009)
Outcome	The authors found that combining both mobilisation with movement (MWM) and kinesiology taping (KT) in patient with Trapeziometacarpal osteoarthritis caused a decrease in reported pain, improved range of motion and improved tip pinch strength. Pre-test on the left hand (untreated), The HADS was 2, right hand (treated) was 2 and post-test was a score of 1. ROM of 1st TMC in palmar abduction with left hand pre-test was 57º, right hand pre-test was 35º, post-test of right hand was 47º and follow up was 50º. ROM of 1st TMC in radial obduction with left hand pre-test was 58º, right hand pre-test was 42º, right hand post-test was 50º and follow up was 50º. PPT (kg/cm²) at TMC joint for left hand pre-test was 4.45, right hand pre-test was 2.18, right hand post-test was 3.75, follow up was 3.9. Tip pinch strength (kg) on left hand pre-test was 3.7, right hand pre-test was 2.14, right hand post-test was 2.5, FU was 2.63. No p values were calculated.
Discussion	The good aspects of this study are that the participant case is well described including the diagnostic criteria and definition of the condition making it easier for future research to replicate it. The author also excluded the effect of medication by mentioning that the patient was not using medication at the initial assessment, the study seems to have been done prospectively which significantly improves the reliability of the outcomes and a balance of objective and subjective measures were used to maximize on the data acquired and limit assessor and participant bias. The main limitations that increased the level of bias in the study is the study was performed as a case report with only one participant and no control group, confounding variables may play a role and would be difficult to control for, selection bias may have occurred, the therapist was also the assessor which can introduce assessor bias and more than one intervention was applied which makes it difficult to know which was the main causative factor. These mentioned factors have all lead to the high level of bias that was found in this study meaning outcomes cannot be accepted except for it to be a guide for future research. Since this study is a case report, it is not applicable in clinical practice. what this study can be used for, is a reference for future research to replicate and possible produce similar beneficial results in a clinical trial. The replication of this study is however limited because of the limited detail on the intervention that were used which would make it difficult to repeat the same intervention in the future.
Conclusion	Based on the limitations of the study which are significant given the case reporting structure, the external validity was highly compromised even though the reviewers provided the study an overall rating of 6/8 using the JBI critical appraisal tool for case reports. In view of this, and since intervention was provided as part of a programme the case report provides no evidence for the intervention. Future studies looking to replicate this study should look at performing a randomized controlled trail which can then be used as an evidence base for information on this method of treatment. Additionally, A single intervention should be administered to the group for results to be relevant.

4.5 CONCLUSION OF CHAPTER FOUR

The purpose of Chapter Four was to present the impact of form and structure of the studies in order to develop an understanding of the external and internal validity and their collective impact on the evidence available through the work done by each or the authors.

Thus, in addition to the ratings that the reviewers gave, which assessed the methodological rigour of studies according to a scale (internal validity), the studies were also further critiqued for their limitations in a qualitative method based on evidence from other studies on quality assessment of studies that indicated what factors increased bias and limited the generalisability of the pertaining study types (external validity).

Chapter Five will now present the information with respect to how these different publications collectively provide evidence in support / not in support of manual therapies (mobilisation and manipulation) in the treatment of OA.

CHAPTER FIVE DISCUSSION OF RESULTS

5.1 INTRODUCTION

From Chapter Four, the level of evidence in support of mobilisation and manipulation is presented by category allowing for a better understanding of the cumulative evidence in each category of treatment (manipulation and mobilisation) for each area being treated (OA of the spine, OA of the hand, OA of the TMJ and OA of the shoulder).

5.2 CRITERIA FOR GRADING EVIDENCE FROM EACH STUDY

The criteria used for grading the evidence was based on the work of Dagenais and Haldeman (2011) and Foley *et al.* (2003) due to ease of understanding and relevance to the studies being graded as compared to the GRADE system (Brozek *et al.* 2009). As mentioned in Chapter Three, both Dagenais and Haldeman (2012) and Foley *et al.* (2003) categorise evidence as high, moderate, low, or no evidence. Foley *et al.* (2003) also has 2 additional categories which are consensus (evidence agrees with each other) and conflicting (evidence conflicts with each other).

With this method of grading described by Dagenais and Haldeman (2012) and Foley *et al.* (2003), the level of evidence that is present for each area using mobilisation or manipulation could be determined and collected according to category for a clearer understanding. The six levels of evidence that were used were as follows:

1. Strong evidence: this occurs when the evidence of studies within one group (e. g. mobilisation or manipulation) is supported by two or more RCTs of at least moderate quality.
2. Moderate evidence: This occurs when the evidence of studies within one group (e. g. mobilisation or manipulation) are supported by one RCT or more of at least moderate quality.
3. Limited Evidence: This occurs when the evidence of studies within one group (e. g. mobilisation or manipulation) is supported by at least one nonexperimental study (e.g., non-randomized controlled trial, cohort study, etc.).
4. No evidence: this occurs if the study is a high-quality study revealing no effect with the intervention or a low-quality study producing little to no evidence.
5. Consensus: this occurs when there is agreement between studies regarding the outcome of the studies within a particular group (e. g. mobilisation or manipulation) which can

either be for or against a particular intervention being used on a particular region of the body.

6. Conflicting evidence: This occurs when there is disagreement in the findings among at least two RCTs within a specific group (e. g. mobilisation or manipulation). However, in the case of where there is only one RCT that contains conflicting results in a group containing many RCTs, the conclusions are based off the majority meaning the evidence is not conflicting.

5.3 RANKING OF EVIDENCE FOR EACH GROUP

5.3.1 Mobilisation

Table 5.1 Mobilisation

Authors	Year	Region treated	Study type	Internal validity	External validity	Authors Outcome (PR: Program)	Collective evidence					
							Strong	Moderate	Limited	Consensus	Conflicting	No evidence
Igatpurikar, P	2013	Lumbar spine	RCT	7/11	Limited to none	PR						
Sharma, A. Alahmari, K. Ahmed, I	2015	Lumbar spine	RCT	7/11	Limited to none	PR						
Bhanushali, V. Jagtap, V. Poovishnu, D.	2017	Lumbar spine	RCT	7/11	Limited to none	PR						
Egwu, M. O.	2008	Cervical spine	nRCT	3/9	Limited	Positive						
Huang, Z. Chen, J. Qi, W	2009	Cervical spine	RCT	5/11	No evidence	PR						
Yu, H. Hou, S. Wu, W. He, X	2011	Cervical spine	CS	5/10	No evidence	PR						
Copurgensli, C. Gur, G. Tunay, V. B.	2017	Cervical spine	RCT	8/11	Limited to none	PR						
Maicki, T. Bilski, J. Szczygieł, E. Trąbk, R.	2017	Cervical spine	RCT	9/11	Limited to none	PR						
Qayyum, S. Waqas, S. Asim, H. M.	2017	Cervical spine	nRCT	0/9	No evidence	PR						
Nicolakis, P. Burak, E. Kollmitzer, J. Kopf, A. Piehslinger, E. Wiesinger, G. Fialka-Moser, V.	2016	TMJ	nRCT	3/9	No evidence	PR			X	X		
Crowell, M. S. Tragord, B. S.	2015	GHJ	CR	7/8	No evidence	PR						
Villafane, J. Cleland, J. Fernandez-de-Las-Penas, C.	2013	Thumb CMC joint	RCT	10/11	Limited to none	PR						
Villafane, J. Langford, D. Alguacil-Diego, I. Fernandez-Carnero, J.	2013	Thumb CMC joint	CR	7/8	No evidence	PR						
Villafañe, J. H. Silva, G. B. Diaz-Parreño, S. A. Fernandez-Carnero, J.	2011	Thumb CMC joint	RCT	9/11	Moderate to high	Positive						
Villafane, J. Silva, G. Chiarotto, S.	2012	Thumb CMC joint	CS	8/10	Limited to none	Positive						
Villafane, J. H. Silva, G. B. Fernandez-Carnero, J	2012	Thumb CMC joint	RCT	9/11	Moderate to high	Positive						

From Table 5.1, it can be seen that the majority of the studies that involve mobilisation of a series of joints or a particular joint, consists of mobilisation with one or more therapy that constitutes a treatment programme as compared to evaluating the effect of mobilisation alone against another modality or placebo / sham intervention. In this context the studies provide no evidence in support of the individual intervention of mobilisation within the context that it is applied. Therefore, for the application of mobilisation for the treatment of OA of the joints associated with the lumbar spine, TMJ and GHJ there is currently no available evidence for the use of mobilisation as an individual treatment modality. This therefore implies that there is a need for more studies that evaluate the use of mobilisation as a stand alone modality within this particular context in order to provide evidence for use of this modality in clinical practice.

In terms of the regions that include the thumb joint (carpometacarpal joint) and the cervical spine, there are collectively more programme based studies than individual assessment of mobilisation for the thumb joint and for the cervical spine.

However, in respect of the of the thumb joint, where there are three studies that evaluated mobilisation alone, it is evident that the level of evidence for mobilisation of this joint is moderate, given that the studies show:

- 2 RCTs.
- High internal validity (8/10, 9/11, 9/11).
- Moderate to high levels of external validity in the two RCTs.
- Positive clinical outcomes with respect to pain and pinch strength.

These outcomes may need to be considered with caution though as the datelines for these studies suggest that the older studies provide greater evidence in favour of the mobilisation as compared to the newer studies, although this is contrasted by the fact that the newer studies are more likely to be case studies as opposed to RCTs. Thus, there is an argument that the sequencing of the publications versus the type of publications, may negate effect of either and that the changes that may impact on these publication types (namely, greater formalization of the reporting checklists for the various studies, improved requirements for these studies in terms of publication submission) may not have resulted in any impact on the outcomes or why these studies in particular were published (reference the most recent Cochrane checklists).

Thus, it could be considered, that the use of mobilisation in the treatment of the thumb's carpometacarpal joint is indicated in clinical practice, especially if the population is

compliant with the population under study (namely, housewives and ex-factory workers that methodically used their dominant hand often, are between 70–90 years of age and were diagnosed with stage three or four CMC OA according to the Eaton-Littler-Burton classification (Eaton and Glickel 1987)). Outside of these patient populations the use of mobilisation needs to be considered with caution, as there is little evidence to support its use.

By comparison in the cervical spine, there were six studies that were included and evaluated for evidence. Of these only one provided evidence in the evaluation of mobilisation as a single intervention for OA of the cervical spine. This single nRCT study provided low internal validity (3/9) and limited evidence as a result of bias due to uncontrolled factors not measured on the scales (resulting in decreased external validity). Therefore, even though the study showed positive clinical outcomes, the compromised structure of the study and the external validity issues reduce the evidence to limited in support of the use of mobilisation for the cervical spine in OA patients. Thus, mobilisation of the cervical spine given the evidence evaluated in this systematic review, indicates that it should not be utilized as a standard care protocol for patients with cervical spine pain (as a result of OA) and that further research is required to confirm or refute the findings that these two studies suggest (Egwu 2008). This is further supported by the fact that the Egwu (2008) study is the oldest of the studies pertaining to the cervical spine and the effect that mobilisation achieves for patients. Thus, the outcomes of the study may be challenged if the study were repeated under more formalized criteria and requirements that may now exist within the research and publication domains at present (namely, greater formalization of the reporting checklists for the various studies, improved requirements for these studies in terms of publication submission) (Higgins *et al.* 2022).

To contextualise the above outcomes, publication bias also needs to be taken into consideration as published work is more likely to be published if the outcomes are positive. This results in an overestimation of the overall effect of a treatment (Dwan *et al.* 2013). Thus, if we account for these unpublished studies, the evidence may actually be even less in support of mobilisation for the thumb CMC and cervical spine than is reported here. This further supports the need for increased publications at every level from case studies to RCTs that directly evaluates the mobilisation in the TMJ, GHJ, spine (cervical and lumbar spine) and thumb CMC joint.

These future studies generally need to consider the following generic short comings, as they open the study to external influence or bias and detract from its ability to test the

intervention accurately (Kendal 2003; Akobeng 2008; Renjith 2017). By addressing these testing of manipulation and mobilisation in the treatment of OA of the spine, TMJ, GHJ and thumb CMC joint becomes more useful and can be extrapolated to either the general population or specific population groups, which will improve clinical practice.

These short comings collectively include:

- Clear inclusion and exclusion criteria with clear description of the patients within each of the groups compared in the study. This includes patient characteristics such as age, gender, occupation, systemic disease profile, medication use (acute and chronic) and medication changes (Kendall 2003). Given that OA is a degenerative condition, it also requires that the patients are at similair stages in their OA presentation for the intervention to be properly tested. Any difference in patient groups could alter outcomes and is likely to show an intervention ineffective (Akobeng 2008; Mahue et al 2006). Exclusion criteria should also be clear and detailed on the contraindications to manipulation as well as exclusions for those that will have significantly lower responses or skew responses such as those with previous surgery (Assmann et al. 2000).
- A priori calculations to find the study power and an adequate sample size needed for results to be due to more than chance was not present in some studies, where as it should be included (Christley 2010).
- statistical significance of an intervention was on some studies not measured which is important to show that the outcomes if significant, are due to more than chance and to highlight the superiority of interventions over another (Pintea 2010).
- A lack of baseline reporting for all outcome measures, along with a tendency to have outcome measures predominantly measuring only subjective clinical outcomes. The latter being subject to a lack of randomization / concealed allocation, assessor blinding, as well as factors related to patient experience / naivety, patient perception, Hawthorne effects, blinding bias, touch therapy impact and therapist patient dynamics that may occur (Sedgwick and Greenwood 2015; Akobeng 2008; Ernst 2007; Kendal 2003). Additionally subjective measures tend to be limited to only reporting pain or impact of pain, when degeneration may also influence other clinical measures such as range of motion, muscle activity and response times to stimuli and various measures of balance and proprioception. These latter measures may actually better measure the impact of mobilisation than necessarily only pain and its impact, thus the current data is skewed in terms of the predominant pain findings.
- Many studies did not detail the treatment protocol adequately making it difficult for it to be reproduced by others.

- The impact of mobilisation for the most part, seems to have only been measured in the short or medium term. The longer term studies did not control for extraneous variable input in terms of trauma for example (through a research diary, or impact diary) and thus the longer term results are also less reliably a measure of the intervention than a combination of many extraneous variables.

In contrast, evidence for OA of the knee and hip has been published in previous systematic reviews (Anwar *et al.* 2018; Beumer *et al.* 2016; Ceballos-laita *et al.* 2019; Chen at al. 2018; Sampath *et al.* 2016). And consideration needs to be given to areas that have no published findings including the thoracic spine and others not noted in this study, as these regions would also benefit from the development of guidelines that either refute or confirm that the use of mobilisation is indeed clinically efficacious and should thus be implemented in clinical practice.

5.3.2 Manipulation

Table 5.2 Articles involving manipulation

Authors	Year	Region treated	Study type	Internal validity	External validity	Authors outcome (PR: Programme)	Collective evidence					
							Strong	Moderate	Limited	Consensus	Conflicting	No evidence
Vieira-Pellenz, F. Oliva-Pascual-Vaca, A. Rodriguez-Blanco, C. Heredia-Rizo, A. Ricard, F. Almazán-Campos, G.	2014	Lumbar Spine	RCT	10/11	Moderate	Positive			X	*		
Sokunbi, O.G.	2015	Cervical spine	CR	6/8	No evidence	PR						
Yu, H. Hou, S. Wu, W. He, X.	2011	Cervical Spine	CS	5/10	no evidence	PR						

*One article does not confer consensus or conflicting evidence

From Table 5.2, two out of the three studies that involve manipulation evaluated the effect of manipulation with one or more therapies constituting a treatment programme compared to evaluating manipulation alone compared to another modality or placebo intervention. In the context of this systematic review, the studies that involve manipulation in a programme provide no evidence in support of the individual intervention of manipulation. Thus, there is

currently no available evidence for the treatment of OA of the cervical spine using manipulation alone as a method of treatment. Which implies that more studies are needed to evaluate the use of manipulation as a stand alone therapy for the treatment of OA of the cervical spine to be used as evidence in clinical practice.

As for the lumbar region. There was a single study that assessed the use of manipulation of the treatment of lumbar spine OA and that study assessed manipulation as a stand alone modality. Therefore, in respect of the lumbar spine there is moderate to limited evidence for the treatment of OA using manipulation alone given that that there was only one study, which was an RCT, had high internal validity (10/11), a moderate level of external validity and gave positive clinical outcomes regarding pain, spinal mobility in flexion, and hip flexion. Therefore, the use of manipulation is indicated with in clinical practice for the treatment of lumbar spine OA, especially men between the age of 18-55 with evidence of lumbosacral disc degeneration and lower back pain. However, outside of this population, it is indicated with caution.

No publications were compliant with the inclusion criteria of this study that reported manipulation of any other spinal region, in addition to wrist, GHJ and TMJ publications involving OA. Therefore, this study can only indicate that the use of manipulation for lumbar spine OA has limited evidence in support of its use, when the Dagenais and Haldeman (2011) and Foley *et al.* (2003) grading systems are applied. Additionally, this study cannot comment on whether the data is conflicting or provides consensus on the use of manipulation in the two spinal regions, as the cervical spine data provides not evidence and the lumbar spine data only provides one study on which to comment. Further to this, publication bias requires consideration as positive outcomes are published more frequently compared to conflicting studies or studies with no evidence, resulting in an overestimation of the overall treatment effect (Dwan *et al.* 2013). Therefore, if the unpublished studies are accounted for, the evidence in support of manipulation for lumbar spine OA may be even lower. This possible publication bias supports the need for more publications at all levels of studies from case reports to RCTs that evaluate manipulation as a stand-alone modality.

Future research, definitively needs to consider increasing publications around manipulation, in order for there to be a debate within this domain of study as to the impact of manipulation on OA of the spine. This would then positively impact the clinical guidelines available to practitioners for implementation of the data in clinical practice (Bernstein 2004).

These studies would however need to consider the short comings of the publications included in this study, which include generally the following thematic areas:

- Greater use of RCT or nRCT study types as opposed to case series or case studies, with the presence of placebo controlled or sham conditions (Bernstein 2004).
- Resultantly, clearer inclusion criteria with clear patient characteristic and condition parameter delineation in order for the treatment / intervention to be the focus of the outcome measures (Kendall 2003).
- Use of randomization tables and concealed allocation (Kendall 2003).
- Use of appropriate *a priori* analysis which underpins the group sizes within the study, allowing improved statistical analysis, in addition to a reduction in type two error based conclusions. This followed by both reporting of statistical and clinical significance would improve the clinical applicability to clinical practice. (Christley 2010; Pintea 2010).
- Reporting all baseline data (from inclusion criteria) as well as for all outcome measures. This would assist in identifying the outcomes as only being contingent on intervention.
- As with mobilisation discussion, having a varied range of outcome measures that do not only allow on reporting of pain and its impact. This will negate the impact of patient experience / naivety, patient perception, Hawthorne effects, blinding bias, touch therapy impact and interpersonal relationships that the researcher / therapist and patient may have (Renjith 2017; Tabatabaee *et al.* 2016; Sedgwick and Greenwood 2015; Akobeng 2008; Ernst 2007).
- Include varied outcome measures such as range of motion, muscle activity and response times to stimuli and various measures of balance and proprioception.
- Consider controlling for patient variables throughout the study with the use of patient diaries for reporting changes not due to the intervention. Additionally considering a range of studies that report on immediate, short- and long-term outcomes.

5.3.3 Neural Mobilization

Table 5.3 Articles involving neural mobilisation

Authors	year	Region treated	Study type	Internal validity	External validity	Outcome	Collective evidence					
							Strong	Moderate	Limited	Consensus	Conflicting	No evidence
Villafane, J. Cleland, J. Fernandez-de-Las-Penas, C.	2013	Thumb CMC joint	RCT	10/11	Limited to none	PR						
Villafañe, J. H. Silva, G. B. Bishop, M. D. Fernandez-Carnero, J.	2012	Thumb CMC joint (wrist)	RCT	9/11	Moderate to limited	Positive			X	X		
Villafane, J. Silva, G. Fernandez-Carnero, J.	2011	Thumb CMC joint	CS	7/10	Limited	Positive						

Table 5.3 shows three studies that involve neural mobilisation for the treatment of thumb CMC joint OA. A majority of two of the three studies evaluated neural mobilisation as a stand alone modality, while one study investigated neural mobilisation combined with other therapies. In terms of neural mobilisation for treating the thumb CMC joint, it is evident that the level of evidence for neural mobilisation is limited in respect of the clinical outcomes of pain and tip pinch strength given that the studies show:

- 1 RCT and 1 CS.
- High internal validity (RCT with 9/11 and CS with 7/11).
- Moderate to limited external validity in the RCT and limited in the CS.

Therefore, neural mobilisation in the treatment of thumb CMC OA requires further evidence for its use to be recommended in clinical practice due to its limited level of evidence. It can be considered with caution if the treated population is compliant with the population under study which included, house workers or ex-factory workers, who used their dominant hand often and methodically, between the ages of 70-90 and were diagnosed with stage three or four secondary thumb CMC joint OA according to the Eaton-Littler-Burton classification (Villafane *et al.* 2012; Villafane *et al.* 2011; Eaton and Glickel 1987).

No other joint or regions in the body can be recommended for neural mobilisation to be used on as the only studies available involve the thumb CMC joint. Further research is needed to confirm or refute the finding that these studies suggest as it is only limited to two

studies (Villafane *et al.* 2012 and Villafane *et al.* 2011) in addition to studies for other regions of the axial and appendicular musculoskeletal frame.

Much like the prior joint mobilisation and joint manipulation sections (Section 5.3.1 and 5.3.2) previously discussed, publication bias also needs to be taken into consideration as positive outcomes are more likely to be published leading to an overestimation of positive outcome reporting (Dwan *et al.* 2013). Therefore, when accounting for the possible unpublished studies, evidence be even less in support of neural mobilisation. Thus, research should be published at all levels from case reports to RCT no matter the outcome that directly evaluate neural mobilisation to prevent this problem.

Future research, definitively needs to consider increasing publications around manipulation, in order for there to be a debate within this domain of study as to the impact of neural mobilisation on OA of thumb CMC joint. This would then positively impact the clinical guidelines available to practitioners for implementation of the data in clinical practice (Bernstein 2004).

These studies would, however, need to consider the short comings of the publications included in this study, which include, generally, the following thematic areas:

- Clearer inclusion criteria with clear participant characteristics such as age, gender, occupation, medication use and medication changes for improved generalization (Kendall 2003).
- Proper baseline measurements of all participant characteristics as well as chosen outcome measures for homogeneity between groups. Homogeneity between groups also requires randomization, concealed allocation.
- Other factors that also need to be considered include patient naivety, Hawthorne effect, blinding bias, effects of touch therapy, choice of placebo, dynamics between therapist and participants, and dynamics between assessors and participants (Renjith 2017; Tabatabaee *et al.* 2016; Sedgwick and Greenwood 2015; Akobeng 2008; Ernst 2007).
- Having a range of different outcome measures that measure more than just pain, such as range of motion, dexterity and muscle activity can also provide further information that can also overcome the effects of placebo, Hawthorne effect, therapist patient dynamics and blinding as they are objective measurements.
- Neural mobilisation also seems to have been measured only in the short/ intermediate term. Long term studies are also needed confirm or refute whether neural mobilisation is effective and should be implemented.

- Intervention protocol should also be clearly described for easy replication as this was a recurring problem and many of the included studies (Kendall 2003).

5.4 CONCLUSION OF CHAPTER

With reference to the previous discussion of intervention types included in this systematic review, Table 5.4 provides a summary.

Table 5.4 Compiled evidence for interventions

Interventions	Collective evidence					
	Strong	Moderate	Limited	Consensus	Conflicting	No evidence
Mobilisation			X	X		
Manipulation			X			
Neural Mobilisation			X	X		

Table 5.4 summarizes the evidence available for each type of modality in the treatment of OA. Based on this table, mobilisation, manipulation and neural mobilisation all provide limited evidence for their use in clinical practice. This low level of evidence was mainly due to many studies being in the form of programmes which did not evaluate mobilisation, manipulation or neural mobilisation as stand-alone interventions. Therefore caution should be taken when recommending these modalities for OA especially when the population does not align with the included study populations.

Within each category there are some regions which contain more evidence, this includes the thumb CMC joint for mobilisation and neural mobilisation as well as the lumbar spine for manipulation. These studies form the basis for the limited evidence, given that other regions that received an intervention for OA did not provide any evidence.

All of the studies included in this systematic review, suffered from the majority of studies being located lower in the research hierarchical pyramid (namely, case studies, case series and nRCTs), with very few RCTs by comparison (Dulay *et al.* 2015). This thus reflects in the shortcomings of the categories of mobilisation, manipulation and neural mobilisation, where the specific shortcomings affecting the evidence that these groups of studies have provided has been highlighted (Sections 5.3.1, 5.3.2, 5.3.3).

An additional limitation that pertains to all manual therapy studies, is the inability to blind therapists, which is known to have an effect on outcomes (Renjith 2017), in addition to the complexity of blinding participants (the best are naïve participants who have no prior knowledge or experience with the manual therapy interventions being tested), however with OA, it is unlikely that the pool of naïve participants is large, given that most would have sought treatment of some kind at some point in the degenerative process that OA represents. This can be seen in some of the studies where patients were recruited from rehabilitation centers (Qayyum *et al.* 2017; Nicolakis *et al.* 2016; Sokunbi 2015; Vallafane *et al.* 2013), aged care facilities (Villafane *et al.* 2012; Villafane *et al.* 2011) and similar points of contact as this increases the likelihood of OA presentation but largely obscures the ability to locate naïve participants.

Finally all the studies in this systematic review fall into the limitation of being in English or having been translated into English, therefore any studies relating to the topic of this systematic review that did not comply with this criterion was excluded. As a result it is not known what data exists in this pool of studies and how it would impact the outcomes attained here (Hartling *et al.* 2017; Morrison *et al.* 2012; Egger *et al.* 2003). Thus it is recommended that future systematic reviews consider the use of multi-lingual reviewers in order to obtain an even more comprehensive view of the published and available data.

Nevertheless, this study provides evidence that a significant amount of research is still required in all areas of joint mobilisation, joint manipulation and neural mobilisation, in order to justify its use in clinical practice. This need for further research is of particular importance as without the required publications and thus guideline development, the hiatus of information leaves the public, the chiropractor/multidisciplinary team and the patient faced with a stark reality that arises from the following points of clinical contact (Bernstein 2004):

- The inability of providing evidence based information to patients, which impacts on the ability of the patient to receive adequate information to provide fully informed consent decisions (Sampath *et al.* 2016; Bernstien 2004).
- the inability to produce clinical practice guidelines which could help the informed consent process (Sampath *et al.* 2016).
- the erosion of multi and inter-disciplinary confidence in relation to the use of mobilisation and manipulation as a modality (Makaram 1995).

CHAPTER SIX CONCLUSION AND RECOMMENDATION

6.1 INTRODUCTION

Chapter Six provides a conclusion on the dissertation and gives recommendations based on the outcomes of Chapter Four and the discussion of Chapter Five.

6.2 CONCLUSION

The purpose of this study was to assess the current evidence that is available for the treatment of OA with manipulation and mobilisation in the form of a systematic review. This began with a systematic search of the literature on chosen databases containing the key words identified for this study. These retrieved articles were then screened for inclusion into this study based on the criteria associated with review of the title, abstract and full publication.

A total of 20 articles were included into the study which were then reviewed by seven reviewers (three per study). Appropriate scales (namely, PeDro scale for RCTS, the NOS for nRCTs, and the JBI scale for case series and case reports), were utilised to report on internal validity / methodological rigour. The internal validity was combined with a qualitative analysis for external validity was also performed. Based on these two evaluations, a conclusion was drawn on the level of evidence that each article provided. Unfortunately, of these articles, 13 included treatment programmes in which manipulation, mobilisation or neural mobilisation were included, thus reducing the effective number of studies to seven, with total of three articles were of low quality, one article was of low-moderate quality, one article was of moderate quality and two articles were of moderate-high quality.

The articles were then grouped into their intervention types in Chapter Five which were mobilisation, manipulation, and neural mobilisation. From this aggregation of data, it was found that:

- Mobilisation had no evidence for the cervical spine, lumbar spine, GHJ and TMJ.
- Mobilisation had moderate evidence for the Thumb CMC joint.
- The data for mobilisation was in consensus.
- Manipulation had no evidence for the cervical spine.
- Manipulation had moderate to limited evidence for the lumbar spine.
- Neural mobilisation had no evidence for any regions besides the thumb CMC OA.

- Neural mobilisation had limited evidence for the thumb CMC Joint.
- The data for neural mobilisation was in consensus.

6.3 RECOMMENDATIONS

6.3.1 Recommendations to Improve This Systematic Review

Future studies should look at having a mock review process (using an article not part of the research included studies) before the reviews commence. This can be helpful regarding reviewers who are unfamiliar with the scale, questions within the scale that may produce disagreement between reviewers and to provide for easier application of scales (Oremus *et al.* 2012). The average percentage of agreement of all 11 articles using the PeDro scale was 92% (an average of eight responses were agreed upon out of 11 questions in each review), using the NOS scale on three articles , an average of 78% was found (an average of three responses were agreed upon out of the nine questions in each article), using the JBI case series scale was 86% (an average of six responses were agreed upon out of the 10 questions in each article) and using the JBI scale for case reports had an average agreement percentage of 80% (average of three responses agreed upon out of eight questions in each article). This shows that disagreement did occur with the reviewers, with the most disagreement occurring with the NOS scale which was also previously found in other studies to produce disagreement between reviewers due to the nature of the questions (Hartling *et al.* 2013).

Another option can be to either develop the NOS for more reliability when used in systematic reviews, or to use another scale for appraising nRCTs as well as case reports which had a low percentage of agreement in this study. To replace the NOS, the Risk of Bias Assessment Tool for Nonrandomized Trials (RoBANS) can be used which was found to be a fair assessment tool for nRCTs with moderate reliability and validity (Kim *et al.* 2013).

n the case of this study, non-English studies were not included into the review process. Future studies should look at including non-English studies into the review process to prevent any form of language bias. Systematic reviews involving alternative medicine are more likely to be affected by the exclusion of non-English articles as there are more relevant studies performed in these fields, while in English studies, there may be only a few studies (Chen 2015; Cai and Zhong 2012; Bogea *et al.* 2009). It has also been found that German investigators are more likely to publish their results in English if their results were positive (Hartling *et al.* 2017). That may mean that studies which may indicate a reduced affect, no

effect or a negative effect may be excluded from the study which could have a significant effect on the final outcome of the review. However, in the vast majority of cases, it was found that restricting the studies to English only versus all languages did not lead to significant changes in the results of prior systematic reviews except in a few studies (4 out 129 systematic reviews) where there were very few relevant studies in English or the published literature had conflicts of interest or questionable vested interest (Hartling *et al.* 2017). The negatives however of using non-English studies is possible translation bias that may occur or bias from the side of the multilingual reviewer who is reviewing the non-English studies.

6.3.2 Recommendations for Future Studies

Future studies should first use the appropriate publication guidelines for the type of study they wish to report, whether it is an RCT (CONSORT) or observational studies (STROBE), or case series/report (CARE checklist) (Gagnier *et al.* 2013). This is important for the study process to be more efficient and for studies to be more complete. This would also add credibility to the studies as well as to the areas of research being studied (Gagnier et al 2013; Schulz *et al.* 2010; Von Elm *et al.* 2007). Additionally, this would make reviews of such studies less ambiguous and simpler facilitation improvements in guidelines more effectively.

Studies should use the most appropriate study design for the intervention being tested whether it is an RCT, nRCT, case series, or case report. Although in most cases, it is said that RCTs are the most appropriate and highest quality of a research trial, RCTs may not be the best option in all cases. When reviewing the care process that involves more than one form of therapy or intervention such as in clinical practice with mobilisation and manipulation, an observation case-cohort design may be better to adequately demonstrate the benefits and harms of a population who are exposed to that care intervention (Cook and Thigpen 2019). RCTs also contain external validity limitations, due to the effort made in controlling confounding variables and having a homogenous samples, the samples are not similar to populations outside of the study and it is just assumed that similar effects will occur outside of the study (Cook and Thigpen 2019).

Another important aspect relates to how the intervention is performed in a RCT versus how it is performed in clinical practice known as treatment fidelity which involves its reliability and validity (Cook and Thigpen 2019). Treatment fidelity is often sacrificed in the case of

RCTs meaning the intervention in the trial does not represent how it is done in clinical practice (Cook and Thigpen 2019).

Future studies depending on study types also need to consider factors that can affect the internal or external validity possibly increasing bias or decreasing the generalizability of the results (see Sections 5.3.1, 5.3.2 and 5.3.3 in Chapter Five that highlight these concerns thematically).

6.3.3 Recommendations for Practitioners

Based on this study, there was limited evidence found for the use of mobilisation, manipulation or neural mobilisation as stand-alone interventions. This limited evidence is due to the majority of the studies investigated being in the form of programmes where mobilisation was included as part of the programme to treat OA (TMJ, cervical spine, lumbar spine GHJ and thumb CMC joint) which provided no evidence in support of the interventions. Of the studies that evaluated mobilisation as a stand-alone intervention, there was limited evidence in support of treating cervical OA with mobilisation, moderate evidence in support of treating thumb CMC OA with mobilisation and no evidence in the other included regions (lumbar spine, TMJ and GHJ). Treating OA of the lumbar spine using manipulation was found to have moderate to limited evidence (only one study) and no evidence in cervical spine OA. Neural mobilisation provided limited evidence in treating thumb CMC joint OA. Caution should be taken when applying mobilisation, manipulation or neural to any of the mentioned regions due to the limited evidence.

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APPENDICES

Appendix A: Database Search Tables

Database: CINAHL						
Search term	Number of articles	Number of articles included	Author	Year	Article title	Study type
Mobilization OR manipulation OR manual therapy AND osteoarthritis OR spondylosis OR Degenerative joint disease OR degenerative disc disease	79	12	Dabholkar, Kumari, Yardi	2014	Comparative Study of Short Term Response between Maitland Mobilization and Mulligan's Mobilization with Movement of Hip Joint in Osteoarthritis of Knee Patients Identified as Per Clinical Prediction Rule	nRCT
			Dunning, Butts, Young, Mourad, Galante, Bliton, Tanner, Fernández-de-las-Peñas	2018	Periosteal Electrical Dry Needling as an Adjunct to Exercise and Manual Therapy for Knee Osteoarthritis: A Multicenter Randomized Clinical Trial	RCT
			Fish, Kretzmann, Brantingham, Globe, Korporaal, Moen	2008	A randomized clinical trial to determine the effect of combining a topical capsaicin cream and knee-joint mobilization in the treatment of osteoarthritis of the knee	RCT
			Harish, Kashif	2013	Effect of Maitland Mobilization and Myofascial Release Technique in Patients with Knee Osteoarthritis	nRCT
			Igatpurikar	2013	Effect of Maitland Spinal Mobilization Therapy Versus Conventional Therapy in Lumbar Spondylosis with Radiculopathy	RCT
			Maicki, Bilski, Szczygieł, Trąbk	2017	PNF and manual therapy treatment results of patients with cervical spine osteoarthritis	RCT
			Narang, Ganvir	2014	Efficacy of Kaltenbohn Mobilization on Patients with Osteoarthritis of Knee Joint	RCT
			Nicolakis, Burak, Kollmitzer, Kopf, Piehslinger, Wiesinger, Fialka-Moser	2001	An investigation of the effectiveness of exercise and manual therapy in treating symptoms of TMJ osteoarthritis	nRCT
			Abdel razek, Shenouda	2014	Efficacy of Mulligan's Mobilization with Movement on Pain, Disability, and Range of Motion in Patients with Knee Osteoarthritis: A Randomized Controlled Pilot Study	RCT
			Sharma	2013	A Randomized Comparison of effectiveness of Clinical Exercises and Manual Therapy Procedures Versus Clinical Exercises alone in the Treatment of Osteoarthritis of Knee	RCT
			Singh	2012	An Experimental Study on effects of Mulligan Mobilization Technique and Isometric Exercises in Patients with Osteoarthritis Knee	RCT
			Sit, Chan, Zou, Chan, Yip, Zhang, Chan, Chung, Reeves, Wong	2018	Clinic-Based Patellar Mobilization Therapy for Knee Osteoarthritis: A Randomized Clinical Trial	RCT

Database: Google Scholar						
Search term	Number of articles	Number of articles included	Author	Year	Article title	Study type
	201	31	Ahmed, Daud	2016	A comparative study between joint mobilization and conventional physiotherapy in knee osteoarthritis	RCT
			Allen, Sheehan, Deyle, Wilken, Gill	2019	A manual physical therapy intervention for symptoms of knee osteoarthritis and associated fall risk: A case series of four patients	Case series
			Brantingham, Parkin-Smith, Cassa, Globe, Globe, Pollard, DeLuca, Jensen, Mayer, Korporaal	2012	Full kinetic chain manual and manipulative therapy plus exercise compared with targeted manual and manipulative therapy plus exercise for symptomatic osteoarthritis of the hip: a randomized controlled trial	RCT
			Crowell, Tragord	2015	Orthopaedic manual physical therapy for shoulder pain and impaired movement in a patient with glenohumeral joint osteoarthritis: a case report	Case report
			Dayle, Henderson, Matekel, Ryder, Garber, Allison	2000	Effectiveness of manual physical therapy and exercise in osteoarthritis of the knee: a randomized, controlled trial	RCT
			Dwyer, Parkin-smith, Brantingham, Korporaal, Cassa, Globe, Bonnefin, Tong	2015	Manual and manipulative therapy in addition to rehabilitation for osteoarthritis of the knee: assessor-blind randomized pilot trial	RCT
			Franklin, Thomas, Dongho, Faustin, Sharma	2018	Conventional Physiotherapy and Additional Krishna's Kinetikinetic Manual Therapy (KKMT) For Knee Osteoarthritis Rehabilitation: A Comparative Study	NRCT
			Giri	2019	The effect of mulligan technique in comparison with maitland mobilization and kinesio taping in patients with osteoarthritis of knee joint	RCT
			hando, Gill, Walker, Garber	2012	Short-and long-term clinical outcomes following a standardized protocol of orthopedic manual physical therapy and exercise in individuals with osteoarthritis of the hip: a case series	Case series
			Ibrahim	2011	Impact of manual therapy, supervised exercises and electro acupuncture versus well-designed home exercise programme on pain and physical function among female patient with knee osteoarthritis: A comparative study	RCT
			Jupudi, Kumar, Mohan	2017	Effects of Mulligan's Mobilization Adjunct to Agility and Perturbation Exercises in Subjects with Knee Osteoarthritis	RCT
			Lam-Tran	2018	A multimodal rehabilitation approach including body weight supported treadmill training, manual therapy, and therapeutic exercise for a patient with hip osteoarthritis	Case series
			Mcdonald, Whiteman, Cleland, Smith, Hoeksma	2006	Clinical outcomes following manual physical therapy and exercise for hip osteoarthritis: a case series	Case series
			Malgaonkar, Kumar, Babu, Rizvi	2014	Short term effect of mulligans mobilization versus kinesio taping on knee pain and disability for osteoarthritis of knee	RCT
			Medeiros, Rocklin	2016	Manual therapy, therapeutic exercise, and hiptrac for patients with hip osteoarthritis: A case series	Case series
			Mutlu, Ercin, Ozdincler, Ones	2018	A comparison of two manual physical therapy approaches and electrotherapy modalities for patients with knee osteoarthritis: a randomized three arm clinical trial	RCT
			Powers	2017	Successful treatment of a patient with knee osteoarthritis using therapeutic exercise and passive mobilization with regard to regional interdependence	Case series
			Raj, Milton	2017	Effectiveness of manual physical therapy and low intensity cycle ergometry in improving pain, stiffness, physical function and functional exercise capacity in adult with osteoarthritis knee	NRCT
			Rangey, Sheth, Vyas	2015	Comparison of Immediate Effect of Two Different Maitland Mobilization Protocols on Pain and Range Of Motion in Subjects with Osteoarthritis of Knee	RCT
			Rhon, Deyle, Gill, Rendeiro	2013	Manual physical therapy and perturbation exercises in knee osteoarthritis	NRCT

			Sambandam, Sailor, Alagesan	2011	Effect of Mulligan Mobilization and Maitland Mobilization in Subjects with Unilateral Tibiofemoral Osteoarthritis-Randomized Controlled Trial	RCT
			Shenouda	2013	Efficacy of Extracorporeal Shock Wave Therapy Versus Mobilization with Movement on Pain, Disability and Range of Motion In Patients With knee Osteoarthritis	RCT
			Sokunbi	2015	Manual Therapy and Acupuncture in the Treatment of Patient with Cervical Spondylosis with Radicular Pain-Case Report	Case report
			Tanvi, Amrita, Deepak, Kopal	2014	Comparison of effect of hip joint mobilization and hip joint muscle strengthening exercises with knee osteoarthritis	NRCT
			Vaishnavi, Rajeeva	2017	A comparative study of Maitland's mobilization along with ultrasound versus proprioceptive exercises along with ultrasound in stage ii and iii osteoarthritis of knee joint	RCT
			Zemadanis, Betsos, Mandalidis	2017	The short and long-term effect of weight-bearing mobilization-with-movement (MWM) and automobilization-MWM techniques on pain and functional status in patients with hip osteoarthritis	RCT
			Akter	2016	Effectiveness of patella mobilization to improve functional activity and decrease pain among knee osteoarthritis patient	RCT
			Bhat	2010	A comparative study between the effectiveness of mulligans mobilization with movement technique and conventional method to reduce pain and improve functional ability in patients with osteoarthritis of knee	RCT
			Chelliah	2010	Effectiveness of combined Maitland mobilization and theraband exercises in subjects with osteoarthritis of knee – An experimental study	NRCT
			Dwyer	2014	The relative effectiveness of three full kinetic chain treatment protocols for osteoarthritis of the knee: manual therapy, rehabilitation and a combination thereof	RCT
			Fish	2002	The effectiveness and relative effectiveness of combining a topical capsaicin cream and knee joint mobilization in the treatment of osteoarthritis of the knee	RCT
			Mehdi	2013	Effectiveness of combined manual physical therapy and exercise in treating osteoarthritis knee	NRCT

Database: Pubmed						
Search terms	Number of articles	Number of articles included	Author	Year	Article Title	Study type
Mobilization OR manipulation OR manual therapy AND osteoarthritis OR spondylosis OR Degenerative joint disease OR degenerative disc disease	86	4	Pawlowska, Rafal, Jakub, Leszek, Agnieszka	2020	The impact of mobilization on hip osteoarthritis	RCT
			Sharma, Alahmari, Ahmed	2015	Efficacy of Manual Therapy versus Conventional Physical Therapy in Chronic Low Back Pain Due to Lumbar Spondylosis. A Pilot Study	RCT
			Villafane, Cleland, Fernandez-de-Las-Penas	2013	The effectiveness of a manual therapy and exercise protocol in patients with thumb carpometacarpal osteoarthritis: a randomized controlled trial	RCT
			Villafane, Silva, Fernandez-Carnero	2012	Effect of thumb joint mobilization on pressure pain threshold in elderly patients with thumb carpometacarpal osteoarthritis	RCT

Database: Scopus						
Search terms	Number of articles	Number of articles included	Author	year	Article title	Study type
Mobilization OR manipulation OR manual therapy AND osteoarthritis OR spondylosis OR Degenerative joint disease OR degenerative disc disease	105	35	Abbott, Chapple, Fitzgerald, Fritz, Childs, Harcombe, Stout	2015	The incremental effects of manual therapy or booster sessions in addition to exercise therapy for knee osteoarthritis: A randomized clinical trial	RCT
			Abbott, Robertson, Chapple, Pinto, Wright, Leon de la Bara, Baxter, Theis, Campbell	2013	Manual therapy, exercise therapy, or both, in addition to usual care, for osteoarthritis of the hip or knee: A randomized controlled trial. 1: Clinical effectiveness	RCT
			Ali, Ahmed, Khan, Soomro	2014	Comparing the effects of manual therapy versus electrophysical agents in the management of knee osteoarthritis	RCT
			Alkhawajah, Alshami	2019	The effect of mobilization with movement on pain and function in patients with knee osteoarthritis: A randomized double-blind controlled trial	RCT
			Bselega, Neto, Albuquerque-Sendin, Hall, Oliveira-Campelo	2016	Immediate effects of hip mobilization with movement in patients with hip osteoarthritis: A randomised controlled trial	RCT
			Bhanushali, Jagtap, Poovishnu	2017	Effect of facetal joint mobilization in lumbar spondylosis	RCT
			Blackman, Atkins	2014	The effect of adding grade B hip mobilization to a muscle strengthening home exercise programme on pain, function, and range of movement in adults with symptomatic early stage hip osteoarthritis: A pilot study for a randomized controlled trial	RCT
			Cliborne, Waonner, Rhon, Judd, Fee, Matekel, Whitman	2004	Clinical hip tests and a functional squat test in patients with knee osteoarthritis: Reliability, prevalence of positive test findings, and short-term response to hip mobilization	NRCT
			Copugensli, Gur, Tunay	2017	A comparison of the effects of Mulligan's mobilization and Kinesio taping on pain, range of motion, muscle strength, and neck disability in patients with Cervical Spondylosis: A randomized controlled study	RCT
			Courtnry, Steffen, Fernandez-De-Las-Penas, Kim, Chmell	2016	Joint mobilization enhances mechanisms of conditioned pain modulation in individuals with osteoarthritis of the knee	RCT
			Courtney, Witte, Chmell, Hornby	2010	Heightened Flexor Withdrawal Response in Individuals With Knee Osteoarthritis Is Modulated by Joint Compression and Joint Mobilization	NRCT
			Crossley, Vicenzino, Lentzos, Schache, Pandy, Ozturk, Hinman	2015	Exercise, education, manual-therapy and taping compared to education for patellofemoral osteoarthritis: A blinded, randomised clinical trial	RCT
			Cruz-Montecinos, Flores-Cartes. Montt-Rodriguez, Pozo, Besoain-Saldana, Horment-Lara	2016	Changes in co-contraction during stair descent after manual therapy protocol in knee osteoarthritis: A pilot, single-blind, randomized study	RCT
			Curreir, Frohlich, Carow, McAndrew, Cliborne, Boyles, Mansfield, Wainner	2007	Development of a clinical prediction rule to identify patients with knee pain and clinical evidence of knee osteoarthritis who demonstrate a favorable short-term response to hip mobilization	NRCT

			Deyle, Allison, Matekel, Ryder, Stang, Gohdes, Hutton, Henderson, Garber	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 program	RCT
			Egwu	2008	Relative Therapeutic Efficacy of Some Vertebral Mobilization Techniques in the Management of Unilateral Cervical Spondylosis: A Comparative Study	NRCT
			Estebanez-de-Meguel, Fortun-Agud, Jimenez-del-Barrio, Caudevilla-Polo, Bueno-Gracia, Tricas-Moreno	2018	Comparison of high, medium and low mobilization forces for increasing range of motion in patients with hip osteoarthritis: A randomized controlled trial	RCT
			Fitzgerald, Fritz, Childs, Brennan, Talisa, Gil, Neilson, Abbott	2016	Exercise, manual therapy, and use of booster sessions in physical therapy for knee osteoarthritis: a multi-center, factorial randomized clinical trial	RCT
			Hoeksma, Dekker, Ronday, Heering, Van Der Lubbe, Vel, Breedveld, Van Den Ende	2004	Comparison of manual therapy and exercise therapy in osteoarthritis of the hip: A randomized clinical trial	RCT
			Huang, Chen, Qi	2009	Clinical research on treatment of vertebroarterial type of cervical spondylosis with 5-step manipulation and traction	RCT
			Karmali	2017	Conservative management of MRI-confirmed knee osteoarthritis with instrument-assisted soft-tissue mobilization, joint manipulation, and platelet-rich plasma	Case series
			Lozos, Manko, Kobza, Para	2019	Manual therapy with cryotherapy versus kinesiotherapy with cryotherapy for knee osteoarthritis: A randomized controlled trial	RCT
			Loudon	1999	Case report: Manual therapy management of hip osteoarthritis	Case report
			Nor Azlin, Lyn	2011	Effects of passive joint mobilization on patients with knee osteoarthritis	RCT
			Poulsen, Hartvigsen, Christensen, Roos, Vach, Overgaard	2013	Patient education with or without manual therapy compared to a control group in patients with osteoarthritis of the hip. A proof-of-principle three-arm parallel group randomized clinical trial	RCT
			Qayyum, Waqas, Asim	2017	Outcomes of mechanical traction and manual therapy in C5-C6 cervical spondylosis for radicular pain relief	NRCT
			Rao, Balthillaya, Prabhu, Kamath	2018	Immediate effects of Maitland mobilization versus Mulligan Mobilization with Movement in Osteoarthritis knee- A Randomized Crossover trial	RCT
			Sit, Chan, Zou, Chan, Yip, Zhang, Chan, Chung, Reeves, Wong	2018	Clinic-based patellar mobilization therapy for knee osteoarthritis: A randomized clinical trial	RCT
			Takasaki, Hall, Jull	2013	Immediate and short-term effects of Mulligan's mobilization with movement on knee pain and disability associated with knee osteoarthritis-A prospective case series	Case series
			Villafane, Langford, Alguacil-Diego, Fermamdez-Carnero	2013	Management of trapeziometacarpal osteoarthritis pain and dysfunction using mobilization with movement technique in combination with kinesiology tape: A case report	Case report
			Villafane, Silva, Bishop, Fernandez-Carnero	2012	Radial nerve mobilization decreases pain sensitivity and improves motor performance in patients with thumb carpometacarpal osteoarthritis: A randomized controlled trial	RCT
			Villafane, Silva, Chiarotto	2012	Effects of passive upper extremity joint mobilization on pain sensitivity and function in participants with secondary	Case series

					carpometacarpal osteoarthritis: A case series	
			Villafane, Silva, Diaz-Parreno, Fernandez-Carnero	2011	Hypoalgesic and motor effects of Kaltenborn mobilization on elderly patients with secondary thumb carpometacarpal osteoarthritis: A randomized controlled trial	RCT
			Villafane, Silva, Fernandez-Carnero	2011	Short-term effects of neurodynamic mobilization in 15 patients with secondary thumb carpometacarpal osteoarthritis	Case series
			Wright, Abbott, Baxter, Cook	2010	The ability of a sustained within-session finding of pain reduction during traction to dictate improved outcomes from a manual therapy approach on patients with osteoarthritis of the hip	RCT

Database: DUT Summons						
Search terms	Number of articles	Number of articles included	Author	Year	Articles title	Study type
Mobilization OR manipulation OR manual therapy AND osteoarthritis OR spondylosis OR Degenerative joint disease OR degenerative disc disease	110	3	Nawaz, Amer, Asim	2017	Grade 1-2 osteoarthritis of knee joint; outcome of combination of Grade 1-2 knee joint mobilization with quadriceps isometrics in patients	NRCT
			Vieira-Pellenz, Oliva-Pascual-Vaca, Rodriguez-Blanco, Heredia-Rizo, Ricard, Almazán-Campos	2014	Short-Term Effect of Spinal Manipulation on Pain Perception, Spinal Mobility, and Full Height Recovery in Male Subjects With Degenerative Disk Disease: A Randomized Controlled Trial	RCT
			Yu, Hou, Wu, He	2011	Upper Cervical Manipulation Combined with Mobilization for the Treatment of Atlantoaxial Osteoarthritis: A Report of 10 Cases	Case series

Appendix B: Master List

	Author	Year	Title	Reference	Study type	Included
1	Bhanushall, Jagtap, Poovishnu	2017	Effect of facetal joint mobilization in lumbar spondylosis	Bhanushali, V. Jagtap, V. Poovishnu, D. 2017. Effect of facetal joint mobilization in lumbar spondylosis. *Asian Journal of Pharmaceutical and Clinical Research*. 10(6):216-218	RCT	YES
2	CopugensII, Gur, Tunay	2017	A comparison of the effects of Mulligan's mobilization and Kinesio taping on pain, range of motion, muscle strength, and neck disability in patients with Cervical Spondylosis: A randomized controlled study	Copurgensli, C. Gur, G. Tunay, V. B. 2017. A comparison of the effects of Mulligan's mobilization and Kinesio taping on pain, range of motion, muscle strength, and neck disability in patients with Cervical Spondylosis: A randomized controlled study. *Journal of Back and Musculoskeletal Rehabilitation.* 30(1):51-62	RCT	YES
3	Crowell, Tragord	2015	Orthopaedic manual physical therapy for shoulder pain and impaired movement in a patient with glenohumeral joint osteoarthritis: a case report	Crowell, M. Tragord, B. 2015. Orthopaedic manual physical therapy for shoulder pain and impaired movement in a patient with glenohumeral joint osteoarthritis: a case report. J*ournal of orthopaedic & sports physical therapy.* 45(6):453-461	Case report	YES
4	Egwu	2008	Comparison of high, medium and low mobilization forces for increasing range of motion in patients with hip osteoarthritis: A randomized controlled trial	Egwu, M. 2008. Relative therapeutic efficacy of some vertebral mobilization techniques in the management of unilateral cervical spondylosis: A comparative study. *Journal of Physical Therapy Science.* 20(2):103-108	NRCT	YES
5	Huang, Chen, Qi	2009	Clinical research on treatment of vertebroarterial type of cervical spondylosis with 5-step manipulation and traction	Huang, Z. Chen, J. Qi, W. 2009. Clinical research on treatment of vertebroarterial type of cervical spondylosis with 5-step manipulation and traction. *Journal of Traditional Chinese Medicine.* 29(4):268-270	RCT	YES
6	Igatpurikar	2013	Effect of Maitland Spinal Mobilization Therapy Versus Conventional Therapy in Lumbar Spondylosis with Radiculopathy	Igatpurikar, P. 2013. Effect of Maitland Spinal Mobilization Therapy Versus Conventional Therapy in Lumbar Spondylosis with Radiculopathy. *Indian Journal of Physiotherapy & Occupational Therapy.* 7(3):177-183	RCT	YES
7	Maicki, Bilski, Szczygieł, Trąbk	2017	PNF and manual therapy treatment results of patients with cervical spine osteoarthritis	Maicki, T. Bilski, J. Szczygieł, E. Trąbk, R. 2017. PNF and manual therapy treatment results of patients with cervical spine osteoarthritis. *Journal of Back & Musculoskeletal Rehabilitation.* 30(5):1095-1101	RCT	YES
8	Nicolakis, Burak, Kollmitzer, Kopf, Piehslinger, Wiesinger, Fialka-Moser	2001	An investigation of the effectiveness of exercise and manual therapy in treating symptoms of TMJ osteoarthritis	Nicolakis, P. Burak, E. C. Kollmitzer, J. Kopf, A. Piehslinger, E. Wiesinger, G. F. Fialka-Moser, V. 2001. An investigation of the effectiveness of exercise and manual therapy in treating symptoms of TMJ osteoarthritis. *CRANIO: The Journal of Craniomandibular & Sleep Practice.* 19(1):26-32	nRCT	YES
9	Qayyum, Waqas, Asim	2017	Outcomes of mechanical traction and manual therapy in C5-C6 cervical spondylosis for radicular pain relief	Qayyum, S. Waqas, S. Asim, H. M. 2017. Outcomes of mechanical traction and manual therapy in C5-C6 cervical spondylosis for radicular pain relief. *Pakistan Journal of Medical and Health Sciences.* 11(3): 1100-1102	NRCT	YES
10	Sharma, Alahmari, Ahmed	2015	Efficacy of Manual Therapy versus Conventional Physical Therapy in Chronic	Sharma, A. Alahmari, K. Ahmed, I. 2015. Efficacy of Manual Therapy versus Conventional Physical Therapy in Chronic Low Back Pain Due to Lumbar	RCT	YES

			Low Back Pain Due to Lumbar Spondylosis. A Pilot Study	Spondylosis. A Pilot Study. *Medical sciences.* 3:55-63		
11	Sokunbi	2015	Manual Therapy and Acupuncture in the Treatment of Patient with Cervical Spondylosis with Radicular Pain-Case Report	Sokunbi, O. 2015. Manual Therapy and Acupuncture in the Treatment of Patient with Cervical Spondylosis with Radicular Pain-Case Report. *Journal of Novel physiotherapies.* 5(3)	Case report	YES
12	Vieira-Pellenz, Oliva-Pascual-Vaca, Rodriguez-Blanco, Heredia-Rizo, Ricard, Almazán-Campos	2014	Short-Term Effect of Spinal Manipulation on Pain Perception, Spinal Mobility, and Full Height Recovery in Male Subjects With Degenerative Disk Disease: A Randomized Controlled Trial	Vieira-Pellenz, F. Oliva-Pascual-Vaca, A. Rodriguez-Blanco, C. Heredia-Rizo, A. Ricard, F. Almazán-Campos, G. 2014. Short-Term Effect of Spinal Manipulation on Pain Perception, Spinal Mobility, and Full Height Recovery in Male Subjects With Degenerative Disk Disease: A Randomized Controlled Trial. *Archives of Physical Medicine and Rehabilitation.* 95(9):1613-1619.	RCT	YES
13	Villafane, Cleland, Fernandez-de-Las-Penas	2013	The effectiveness of a manual therapy and exercise protocol in patients with thumb carpometacarpal osteoarthritis: a randomized controlled trial	Villafane, J. Cleland, J. Fernandez-de-Las-Penas, C. 2013. The effectiveness of a manual therapy and exercise protocol in patients with thumb carpometacarpal osteoarthritis: a randomized controlled trial. *Journla of orthopaedic & Sports physical therapy.* 43(4):204-213	RCT	YES
14	Villafane, Langford, Alguacil-Diego, Fermamdez-Carnero	2013	Management of trapeziometacarpal osteoarthritis pain and dysfunction using mobilization with movement technique in combination with kinesiology tape: A case report	Villafañe, J. H. Langford, D. Alguacil-Diego, I. M. Fernández-Carnero, J. 2013. Management of trapeziometacarpal osteoarthritis pain and dysfunction using mobilization with movement technique in combination with kinesiology tape: A case report. *Journal of Chiropractic Medicine.* 12(2): 79-86	Case report	YES
15	Villafane, Silva, Bishop, Fernandez-Carnero	2012	Radial nerve mobilization decreases pain sensitivity and improves motor performance in patients with thumb carpometacarpal osteoarthritis: A randomized controlled trial	Villafañe, J. H. Silva, G. B. Bishop, M. D. Fernandez-Carnero, J. 2012. Radial nerve mobilization decreases pain sensitivity and improves motor performance in patients with thumb carpometacarpal osteoarthritis: A randomized controlled trial. *Archives of Physical Medicine and Rehabilitation.* 93(3):396-403.	RCT	YES
16	Villafane, Silva, Chiarotto	2012	Effects of passive upper extremity joint mobilization on pain sensitivity and function in participants with secondary carpometacarpal osteoarthritis: A case series	Villafañe, J. H. Silva, G. B. Chiarotto, A. 2012. Effects of passive upper extremity joint mobilization on pain sensitivity and function in participants with secondary carpometacarpal osteoarthritis: A case series. *Journal of Manipulative and Physiological Therapeutics.* 35(9):735-742.	Case series	YES
17	Villafane, Silva, Diaz-Parreno, Fernandez-Carnero	2011	Hypoalgesic and motor effects of Kaltenborn mobilization on elderly patients with secondary thumb carpometacarpal osteoarthritis: A randomized controlled trial	Villafañe, J. H. Silva, G. B. Diaz-Parreño, S. A. Fernandez-Carnero, J. 2011. Hypoalgesic and motor effects of Kaltenborn mobilization on elderly patients with secondary thumb carpometacarpal osteoarthritis: A randomized controlled trial. *Journal of Manipulative and Physiological Therapeutics.* 34(8):547-556.	RCT	YES
18	Villafane, Silva, Fernandez-Carnero	2012	Effect of thumb joint mobilization on pressure pain threshold in elderly patients with thumb carpometacarpal osteoarthritis	Villafane, J. H. Silva, G. B. Fernandez-Carnero, J. 2012. Effect of thumb joint mobilization on pressure pain threshold in elderly patients with thumb carpometacarpal osteoarthritis. *Journal of Manipulative and Physiological Therapeutics.* 35(2):110-120	RCT	YES

19	Villafane, Silva, Fernandez-Carnero	2011	Short-term effects of neurodynamic mobilization in 15 patients with secondary thumb carpometacarpal osteoarthritis	Villafañe, J. H. Silva, G. B. Fernandez-Carnero, J. 2011. Short-term effects of neurodynamic mobilization in 15 patients with secondary thumb carpometacarpal osteoarthritis. *Journal of Manipulative and Physiological Therapeutics.* 34(7);449-456	Case series	YES
20	Yu, Hou, Wu, He	2011	Upper Cervical Manipulation Combined with Mobilization for the Treatment of Atlantoaxial Osteoarthritis: A Report of 10 Cases	Yu, H. Hou, S. Wu, W. He, X. 2011. Upper Cervical Manipulation Combined with Mobilization for the Treatment of Atlantoaxial Osteoarthritis: A Report of 10 Cases. *Journal of Manipulative and Physiological Therapeutics.* 34(2):131-137	Case series	YES

Appendix C: Memorandum of Agreement

Dear Prospective reviewer,

Re: Memorandum of Agreement

Title of study: A systematic review on the effectiveness of manipulation and mobilisation in the treatment of osteoarthritis
Principle investigator: Mr Ahmed Khamissa (Researcher)
Co-investigator: Dr C. Korporaal M.Tech:Chiropractic (Supervisor)

Brief introduction and description of the study:
This study is a systematic review or literature related to the use of mobilisation and manipulation in the treatment of osteoarthritis. All literature are collected from online databases by the researcher. All articles in this study are divided in into their study type; randomized controlled trial, non-randomised controlled trial, observation studies, case reports and case series. The articles will be reviewed by external reviewers using scales and checklists pertaining to that study type. Results of reviews will then be collected and presented.

Outline of procedure:
Reviewers will receive articles and the appropriate scales (RCTs – PeDro scale; nRCTs, observational studies, case reports/series – Newcastle Ottawa scale) according to their study type. They will also receive and a detailed explanation for each scale provided. A predetermined time will be given for the completion of assigned articles and the reviewers will then review each articles according to the scale provided. review sheets will then be collected to be statistically analyzed.

Reviewer requirement:
A CV outlining qualification and experience will obtained from each reviewer on agreement to partake in the study. This will be needed for record's sake to support that the proposal guidelines have been followed.

Benefits:
Publication of the study. Should the study be published, all reviewers participating in the study will be included as authors in the publication. Should the reviewer wish to not be included, please cross out this paragraph and initial next to it.

Remuneration:

An honorarium of R 1000.00 is awarded to each reviewer on for appreciation of their time and effort in this review.

Contact persons:

Please do not hesitate to contact either the researcher or supervisor regarding any questions or queries via the following methods

Ahmed Khamissa (researcher):

Cell no: 081 350 5611 Email: ahmedskhamissa@gmail.com

Dr Charmaine Korporaal (Supervisor):

Telephone: 031 373 2611

Cell no: 083 246 3562 Email: Charmak@dut.ac.za

Statement of agreement to participate in the research study:

I …….(Subject's full name).

…….(Identity number / Passport number – only utilized for purposes of a random audit to verify your participation as a reviewer in this study), have read this document in its entirety and understand its contents. Where I have had any questions or queries, they have been explained to me to my satisfaction

Furthermore, I voluntarily agree to participate in this study as a reviewer.

Reviewers name

Reviewers Signature:……. Date:……..

Supervisor name

Supervisor Signature:…….. Date:……

Researcher name

Researcher Signature:…….. Date:……..

Copies of the signed document will also be sent to the reviewers for reference.

Appendix D: PEDro Scale

PEDro scale

The PEDro scale is used for rating the methodological quality of randomized controlled trials. taken from http://www.pedro.org.au.

Reviewer			
Authors			
Year			
Title			
Criterion:		Answer (YES/NO)	Where
1	Eligibility criteria were specified		
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)		
3	Allocation was concealed		
4	The groups were similar at baseline regarding the most important prognostic indicators		
5	There was blinding of all subjects		
6	There was blinding of all therapists who administered the therapy		
7	There was blinding of all assessors who measured at least one key outcome		
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups		
9	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”		
10	The results of between-group statistical comparisons are reported for at least one key outcome		
11	The study provides both point measures and measures of variability for at least one key outcome		
	Total Score		

Appendix E: PEDro Scale Manual

Pedro scale manual

The purpose of the PEDro scale is to help the users of the PEDro database rapidly identify which of the suspected randomised clinical trials are internally valid (criteria 2-9) and could have sufficient statistical information to make their results interpretable (criteria 10-11). A single study can receive a maximum score of 11 satisfying all criterion.

Notes on administration of the PEDro scale:

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	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.
Criterion 2	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-randomisation allocation procedures such as allocation by hospital record number or birth date, or alternation, do not satisfy this criterion.
Criterion 3	*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 4	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.
Criteria 4, 7-11	*Key outcomes* are those outcomes which 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 5-7	*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 8 — 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 9 — 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 10 — 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 ´ time interaction). The comparison may be in the form 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 11 — 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, SDs 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 SDs or SEs). 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

Appendix F: Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Reviewer			
Author			
Year			
Title			
Criteria:			Response
Selection:	1. Is the case definition adequate?	a) yes, with independent validation □	
		b) yes, eg record linkage or based on self reports	
		c) no description	
	2. Representativeness of the cases	a) consecutive or obviously representative series of cases □	
		b) potential for selection biases or not stated	
	3. Selection of controls	a) community controls □	
		b) hospital controls	
		c) no description	
	4. Definition of controls	a) no history of disease (endpoint) □	
		b) no description of source	
Comparability:	1. Comparability of cases and controls on the basis of the design or analysis	A) study controls for___(Select the most important factor.) □	
		b) study controls for any additional factor □ (This criteria could be modified to indicate specific control for a second important factor.)	
Exposure:	1. Ascertainment of exposure	a) secure record (eg surgical records) □	
		b) structured interview where blind to case/control status	
		c) interview not blinded to case/control status	
		d) written self report or medical record only	
		e) no description	
	2. Same method of ascertainment for cases and controls	a) yes □	
		b) no	
	3. Non-response rate	a) same rate for both groups □	
		b) non respondents described	
		c) rate different and no designation	
TOTAL SCORE OUT OF 9:			

Appendix G: Manual for the Newcastle-Ottawa Scale

Selection

1) Is the case definition adequate
    a. Requires some independent validation (e.g. >1 person/record/time/process to extract information, or reference to primary record source such as x-rays or medical/hospital records) *
    b. Record linkage (e.g ICD codes in database) or eslf report with no reference to primary record
    c. No description

2) Representativeness of the cases
    a. All eligible cases with outcomes of interest over a defined period of time, all cases in a defined catchment area all cases in a defined hospital or clinic, group of, health maintenance or organization or an appropriate sample of the those cases (e,g random sample) *
    b. Not satisfying requirements in part (a), or not stated.
3) Selection of controls

    This item assesses whether the control series used in the study is derived from the same population as the cases and essentially would have been cases had the outcome been present.
    a. Community controls (i.e. same community as cases and would be cases if had outcome) *
    b. Hospital controls, within same community as cases (i.e. not another city) but derived from a hospitalised population
    c. No description
4) Definition of controls
    a. If cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded. *
    b. No mention of history of outcome

Comparability

1) Comparability of Cases and Controls on the Basis of the Design or Analysis

A maximum of 2 stars can be allotted in this category

Either cases and controls must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the odds ratio for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never

Age = * Other controlled factors = *

Exposure

1) Ascertainment of exposure

   Stars allocated as per rating sheet

2) Non-response rate

   Stars allocated as per rating sheet

Appendix H: JBI Critical Appraisal Checklist for Case Series

Checklist was obtained from: https://jbi.global/critical-appraisal-tools

Reviewer	
Author/s	
Title	
Year	

Criteria	yes	no	unclear	Not applicable
1. Were there clear criteria for inclusion in the case series?				
2. Was the condition measured in a standard, reliable way for all participants included in the case series?				
3. Were valid methods used for identification of the condition for all participants included in the case series?				
4. Did the case series have consecutive inclusion of participants?				
5. Did the case series have complete inclusion of participants?				
6. Was there clear reporting of the demographics of the participants in the study?				
7. Was there clear reporting of clinical information of the participants?				
8. Were the outcomes or follow up results of cases clearly reported?				
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?				
10. Was statistical analysis appropriate?				
Total				

Appendix I: JBI Case Series Critical Appraisal Tool Manual

Answers: Yes, No, Unclear or Not/Applicable

Each yes equates to 1 point. A no, unclear, or not applicable equates to a 0. The Maximum score attainable is 10/10

1. Were there clear criteria for inclusion in the case series?

The authors should provide clear inclusion (and exclusion criteria where appropriate) for the study participants. The inclusion/exclusion criteria should be specified (e.g., risk, stage of disease progression) with sufficient detail and all the necessary information critical to the study.

2. Was the condition measured in a standard, reliable way for all participants included in the case series?

The study should clearly describe the method of measurement of the condition. This should be done in a standard (i.e. same way for all patients) and reliable (i.e. repeatable and reproducible results) way.

3. Were valid methods used for identification of the condition for all participants included in the case series?

Many health problems are not easily diagnosed or defined and some measures may not be capable of including or excluding appropriate levels or stages of the health problem. If the outcomes were assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If the outcomes were assessed using observer reported, or self-reported scales, the risk of over- or under-reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity.

4. Did the case series have consecutive inclusion of participants?

Studies that indicate a consecutive inclusion are more reliable than those that do not. For example, a case series that states ‘we included all patients (24) with osteosarcoma who presented to our clinic between March 2005 and June 2006’ is more reliable than a study that simply states ‘we report a case series of 24 people with osteosarcoma.’ Studies must state that there was consecutive inclusion of patients that met the inclusion criteria between a specified period of time.

5. Did the case series have complete inclusion of participants?

The completeness of a case series contributes to its reliability (1). Studies that indicate a complete inclusion are more reliable than those that do not. A stated above, a case series that states, ‘we included all patients (24) with osteosarcoma who presented to our clinic between March 2005 and June 2006’ is more reliable than a study that simply states ‘we

report a case series of 24 people with osteosarcoma.' A study must state whether there were any participant drop outs and was there a reason given for them dropping out. If there were no participants dropping out, it must clearly be mentioned that all participants were included in all outcomes measured.

6. Was there clear reporting of the demographics of the participants in the study?

The case series should clearly describe relevant participant's demographics such as the following information where relevant: participant's age, sex, education, geographic region, ethnicity, time period, education.

7. Was there clear reporting of clinical information of the participants?

There should be clear reporting of clinical information of the participants such as the following information where relevant: disease status, comorbidities, stage of disease, previous interventions/treatment, results of diagnostic tests, etc.

8. Were the outcomes or follow-up results of cases clearly reported?

The results of any intervention or treatment should be clearly reported in the case series. A good case study should clearly describe the clinical condition post-intervention in terms of the presence or lack of symptoms. The outcomes of management/treatment when presented as images or figures can help in conveying the information to the reader/clinician. It is important that adverse events are clearly documented and described, particularly a new or unique condition is being treated or when a new drug or treatment is used. In addition, unanticipated events, if any that may yield new or useful information should be identified and clearly described.

9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?

Certain diseases or conditions vary in prevalence across different geographic regions and populations (e.g. women vs. men, sociodemographic variables between countries). The study sample should be described in sufficient detail so that other researchers can determine if it is comparable to the population of interest to them.

10. Was statistical analysis appropriate?

As with any consideration of statistical analysis, consideration should be given to whether there was a more appropriate alternate statistical method that could have been used. The methods section of studies should be detailed enough for reviewers to identify which analytical techniques were used and whether these were suitable.

Appendix J: JBI Critical Appraisal Checklist for Case Reports

The checklist was obtained from: https://jbi.global/critical-appraisal-tools

Reviewer					
Author					
Title					
Year					
Criteria		Yes	No	Unclear	n/a
1. Were patient's demographic characteristics clearly described?					
2. Was the patient's history clearly described and presented as a timeline?					
3. Was the current clinical condition of the patient on presentation clearly described?					
4. Were diagnostic tests or assessment methods and the results clearly described?					
5. Was the intervention(s) or treatment procedure(s) clearly described?					
6. Was the post-intervention clinical condition clearly described?					
7. Were adverse events (harms) or unanticipated events identified and described?					
8. Does the case report provide takeaway lessons?					
Total score					

Appendix K: JBI Case Report Critical Appraisal Tool Manual

Answers: Yes, No, Unclear or Not/Applicable

Each yes equates to 1 point. A no, unclear, or not applicable equates to a 0. The Maximum score attainable is 8/8

1. Were patient's demographic characteristics clearly described?
Does the case report clearly describe patient's age, sex, race, medical history, diagnosis, prognosis, previous treatments, past and current diagnostic test results, and medications? The setting and context may also be described.

2. Was the patient's history clearly described and presented as a timeline?
A good case report will clearly describe the history of the patient, their medical, family and psychosocial history including relevant genetic information, as well as relevant past interventions and their outcomes.

3. Was the current clinical condition of the patient on presentation clearly described?
The current clinical condition of the patient should be described in detail including the uniqueness of the condition/disease, symptoms, frequency and severity. The case report should also be able to present whether differential diagnoses was considered.

4. Were diagnostic tests or methods and the results clearly described?
A reader of the case report should be provided sufficient information to understand how the patient was assessed. It is important that all appropriate tests are ordered to confirm a diagnosis and therefore the case report should provide a clear description of various diagnostic tests used (whether a gold standard or alternative diagnostic tests). Photographs or illustrations of diagnostic procedures, radiographs, or treatment procedures are usually presented when appropriate to convey a clear message to readers.

5. Was the intervention(s) or treatment procedure(s) clearly described?
It is important to clearly describe treatment or intervention procedures as other clinicians will be reading the paper and therefore may enable clear understanding of the treatment protocol. The report should describe the treatment/intervention protocol in detail; for e.g. in pharmacological management of dental anxiety - the type of drug, route of administration, drug dosage and frequency, and any side effects.

6. Was the post-intervention clinical condition clearly described?

A good case report should clearly describe the clinical condition post-intervention in terms of the presence or lack thereof symptoms. The outcomes of management/treatment when presented as images or figures would help in conveying the information to the reader/clinician.

7. Were adverse events (harms) or unanticipated events identified and described?

With any treatment/intervention/drug, there are bound to be some adverse events and, in some cases, they may be severe. It is important that adverse events are clearly documented and described, particularly when a new or unique condition is being treated or when a new drug or treatment is used. In addition, unanticipated events, if any that may yield new or useful information should be identified and clearly described.

8. Does the case report provide takeaway lessons?

Case reports should summarize key lessons learned from a case in terms of the background of the condition/disease and clinical practice guidance for clinicians when presented with similar cases

Appendix L: Research Acceptance Letter

DUT DURBAN UNIVERSITY OF TECHNOLOGY

FACULTY OF HEALTH SCIENCES

12 November, 2020

Mr A Khamissa
Student No: 21515057

Apt 605
199 Playfair Road
Durban
4001

Dear Mr Khamissa

MASTER OF TECHNOLOGY: CHIROPRACTIC

I am pleased to advise that:

1. The Faculty Research Committee approved the following:

    (i) Your research proposal and dissertation title, being:

A systematic review on the effectiveness of manipulation and mobilisation in the treatment of osteoarthritis.

Please note: ANY PROPOSED CHANGES in the DISSERTATION TITLE require the approval of your supervisor and the Faculty Research Committee.

    (ii) Supervisor – **Dr C Korporaal**

2. Your request for funding totalling **R 8 000.00** subject to any literature referred to in Section A of the PG 4a form being accessioned by this University, and any equipment purchased shall become the property of the department.

NOTE: - This funding is not paid directly to you but is controlled by the Faculty Office. Any proposed changes to this funding allocation needs the approval of your supervisor, and Faculty Research Committee

The University Research Committee has stipulated that:

(a) Ownership of any patent registered in respect of the results of your Master's studies is retained by you as the initiator of the project;

(b) Should you make any drift from the results of your Master's studies, you will be required to repay pro rata, the **R 8 000.00** investment which the University Research Committee has made in approving your request for funding:

(c) If the Durban University of Technology provided the equipment/materials for the creation of artefacts, this cost would be refunded to the University if such artefacts were sold and

(d) Durban University of Technology is given first refusal in respect of any possible future sale by you of any patent that may be registered in respect of your said project.

(e) All journal articles, referenced in your dissertation, are to accompany your ring-bound copies when submitting for examination purposes.

Should you experience any problems relating to your research studies, your supervisor must be informed as soon as possible. If the difficulty persists, you must then approach your Head of Department and thereafter the Executive Dean of the Faculty.

Yours sincerely

Ms S Perumal
FACULTY RESEARCH OFFICER

Student's signature in acceptance of the conditions contained herein.

15/01/2021
Date:

Appendix M: DALRO Copyright Quotation

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P O Box 31627
2017 Braamfontein
Telephone 086 12 DALRO
International +27 (0)11 712 8000
Fax +27 (0)86 648 6299

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TO: DURBAN UNIVERSITY OF TECHNOLOGY

Intellectual Property
Durban University of Technology
P O Box 1334
DURBAN

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018/ 018	**JOURNAL OF MANIPULATIVE AND PHYSIOLOGICAL THERAPEUTICS** UPPER CERVICAL MANIPULATION COMBINED WITH MOBILIZATION FOR THE TREATMENT OF ATLANTOAXIAL OSTEOARTHRITIS: A REPORT OF 10 CASES (YU H. {et al}) 159021	2	7	14	R1.07	R42.63 *	R6.39	R49.02
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This Quotation is valid for 90 days.

Appendix N: Prospero Registration

CRD-REGISTER <irss505@york.ac.uk> Dec 24, 2020, 10:01 AM

to Ahmedskhamissa

Dear Mr Khamissa,

We apologise for the delay in dealing with your registration, an ever-increasing number of applications has led to a backlog and substantial delays for some users.

PROSPERO is currently prioritising submissions related to COVID-19. To enable us to focus on these submissions, and to avoid additional delay, during the pandemic we will automatically publish submissions that have been waiting more than 30 days for registration.

This applies to your systematic review "A systematic review on the effectiveness of manipulation and mobilisation in the treatment of osteoarthritis" which was published on our website on Dec 24, 2020.

The records will be published exactly as submitted, without review by the PROSPERO team, so the public record will indicate:

"To enable PROSPERO to focus on COVID-19 registrations during the 2020 pandemic, this registration record was automatically published exactly as submitted. The PROSPERO team has not checked eligibility"

Review owners have always been responsible for the quality and content of PROSPERO records, and high-quality well-written records will continue to speak for themselves.

Your registration number is: CRD42020220697

You are free to update the record at any time, all submitted changes will be displayed as the latest version with previous versions available to public view. Please also give brief details of the key changes in the Revision notes facility and remember to update your record when your review is published. You can log in to PROSPERO and access your records at https://www.crd.york.ac.uk/PROSPERO

Best wishes for the successful completion of your review.

Yours sincerely,

PROSPERO Administrator
Centre for Reviews and Dissemination
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t: +44 (0) 1904 321049
e: CRD-register@york.ac.uk
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Other non-commercial resources that may be of interest
SRDR-Plus is a systematic review data management and archival tool that is available free of charge http://srdrplus.ahrq.gov.

Appendix O: Prisma Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	X
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	X
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	X
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	X
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	X
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	X
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	X
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	X
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	X
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	X
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	X
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	X
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	X
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	X
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	X
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	X
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	X
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	X
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	X
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	X
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	X

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