EVALUATING THE FEASIBILITY OF A NURSE-LED COMPLEX PACKAGE OF CARE FOR KNEE PAIN

Polykarpos Angelos Nomikos, B.Sc., M.Sc.

Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy (PhD)

April, 2022

Declaration

I, Polykarpos Angelos Nomikos, confirm the originality of the work that is presented in thisthesis. Where information has been taken from other sources, I confirm that this has beenshown in the thesis. This thesis has not been accepted for any other degree, diploma, or other qualification. All authors and their contributions to which reference has been made are fully acknowledged.

The following work was carried out at the Department of Academic Rheumatology, City Hospital, Nottingham under the supervision of Professor Abhishek Abhishek, Dr. Michelle Hall, Professor Roshan das Nair and Professor Ana Valdes. This work forms part of a larger project (nested research) that aims to develop and evaluate the feasibility of undertakinga future randomised controlled trial.

Study design, literature search, systematic review, data collection, data analysis, and thesis writing were conducted by myself under the supervision of Professor Abhishek Abhishek, Dr. Michelle Hall, Professor Roshan das Nair. Dr. Amy Fuller (qualitative researcher) guided me through the process of qualitative data collection and analysis. Dr.Michelle Hall was the independent rater for the video assessment of fidelity and providedsupport as the second reviewer for the systematic review. Dr. Bonnie Millar contributed tothe recruitment of the study. Dr. Reuben Ogollah provided statistical advice for fidelity assessment.

This Ph.D. research was funded by the Nottingham NIHR Biomedical Research Centre.

Acknowledgments

First and foremost, I would like to thank Professor Abhishek Abhishek for being a brilliant supervisor and mentor throughout my career and life. Thank you for providing me with the opportunity to undertake this Ph.D. and research. I also extend my sincere thanks to Dr. Michelle Hall for her excellent support and training during the systematic review and the fidelity study. I would not have developed as such without your guidance and patience.

I am also grateful to Dr. Amy Fuller for the guidance with the qualitative data collection and analysis. I am very thankful to Professor Roshan das Nair and Professor Ana Valdes for their guidance, support, and feedback within the qualitative study and fidelity assessment respectively. Moreover, I would like to thank Emeritus Professor Michael Doherty and Professor David Walsh for providing me with feedback during the publicationprocesses and to Dr. Bonnie Millar for contributing to study recruitment.

I take this opportunity to express my gratitude to all the members that took part in the study and especially the nurse who delivered the intervention.

I am very grateful to my family and especially my brother for his endless love and support, for boosting my confidence, and for believing in me throughout this challenging journey.

Finally, I would like to express my gratitude and appreciation to my funding sponsors Biomedical Research Centre and the University of Nottingham for being a host institution of this project for these three and a half years.

Abstract

Background: Non-pharmacological interventions such as education, exercise, and weight loss (if necessary) are core to the management of Osteoarthritis (OA). The role of nurses in managing symptomatic knee OA has been advocated but whether nurses can deliver such interventions as a complex package of care is unknown. The overall aim of this research was to develop and test the feasibility of a nurse-led complex intervention for knee pain comprising non-pharmacological and pharmacological components. The specific objectives of this thesis were to:

1) Systematically review the literature evaluating complex interventions for knee pain due to OA,

2) Evaluate fidelity of delivery of a nurse-led non-pharmacological complex intervention for knee pain,

3) Assess the acceptability of the non-pharmacological component of the intervention, issues faced in delivery, and resolve possible challenges.

Methods: Systematic review and meta-analysis of complex interventions for knee pain due to OA: A systematic literature search was conducted on MEDLINE, EMBASE, AMED, PsycINFO, and CINAHL up until September 29th, 2020. Randomised Controlled Trials (RCTs) comprising at least patient education, exercise, and weight loss interventions were searched. Data were extracted by a single reviewer and cross-checked by two others. Standardised mean differences (SMD) and 95% confidence intervals (CI) were calculated using the random-effects model. The risk of bias was assessed with the Revised Cochrane risk-of-bias tool, and intervention reporting with the template for intervention description and replication (TIDieR) checklist. The primary outcome of interest was knee pain.

Package development phase: 18 participants with knee pain (five with mild severity, eightwith moderate, and five with severe) participated in a single-arm study. The fidelity and acceptability of a nurse-led non-pharmacological intervention comprising assessment, education, exercise, use of hot/cold treatments, footwear modification, walking aids, andweight-loss advice (if required), delivered in 4 sessions over 5 weeks were evaluated.

Fidelity of delivery of intervention: Each intervention session with every participant was video recorded and formed part of the fidelity assessment. Self-reported fidelity checklistswere completed by the research nurse after each session and by an independent researcher, after viewing the video recordings blinded to nurse ratings. Fidelity scores (%), percentage agreement, and 95% Confidence Intervals (CI) were calculated. Two semi-structured interviews were conducted with the research nurse.

Acceptability assessment of the non-pharmacological components: Eighteen adults with chronic knee pain (defined as pain for longer than three months) were recruited from thecommunity. The intervention comprised holistic assessment, education, exercise, weight-loss advice (where appropriate), and advice on adjunctive treatments such as hot/cold treatments, footwear modification, and walking aids. Participants had one-to-one semi- structured interviews at the end of the intervention. The nurse was interviewed after the last visit of the last participant. These were audio-recorded and transcribed verbatim. Themes were identified by one author (PAN) using framework analysis of the transcripts and cross-checked by another (AF).

Results: *Systematic review ad meta-analysis of complex interventions:* We reviewed 2,649 titles and abstracts in the systematic search. The screening process identified twenty RCTs recruiting 3,069 participants with knee OA. Twelve RCTs were included in the meta-analysis. More than half of the studies were judged to be of high quality. The

completenessof intervention reporting was poor. Complex interventions for OA produced moderate benefit for pain relief (-0.47, 95% CI -0.77, -0.16) and physical function (-0.49, 95% CI
-0.72, -0.25). However, studies delivering non-pharmacological interventions for knee OArarely reported both fidelity of delivery and acceptability of non-pharmacological interventions.

Fidelity of delivery of intervention: Fourteen participants completed all visits. 62 treatmentsessions took place. Nurse self-report and assessor video rating scores for all 62 treatmentsessions were included in the fidelity assessment. Overall fidelity was higher on nurse self-report (97.7%) than on objective video-rating (84.2%). The percentage agreement between nurse self-report and video-rating was 73.3% (95% CI: 71.3 - 75.3). Fidelity was
lowest for advice on footwear and walking aids. The nurse reported difficulty advising on thermal treatments, footwear, and walking aids, and did not feel confident negotiating achievable and realistic goals with participants. The nurse found the discussion of goal setting to be challenging.

Acceptability assessment of the non-pharmacological components: Most participants found the advice from the nurse easy to follow and were satisfied with the package, though somefelt that too much information was provided too soon. The intervention changed their perception of managing knee pain, learning that it can be improved with self-management. However, participants thought that the most challenging part of the intervention was fittingthe exercise regime into their daily routine.

Conclusion: A non-pharmacological package of care comprising patient education, exercise, and weight loss advice is more beneficial than usual care or any other single non-pharmacological component. A trained research nurse could deliver such a non-pharmacological package of care with high fidelity and acceptability for the participants

and the nurse delivering the intervention. Future research should consider measuring thefidelity of delivery of intervention and acceptability in a real-world primary-care setting before evaluating it further in a multicentre RCT. Measuring the extent to which components are delivered as intended across different settings and populations, fidelity research may assist to understand which intervention components are effective and in which situations.

List of Publications

Published Papers

Nomikos, P.A., Hall, M., Fuller, A., Millar, B., Ogollah, R., Valdes, A., Doherty, M., Walsh, D.A., Das Nair, R., and Abhishek, A., 2021. Fidelity assessment of nurse- led non-pharmacological package of care for knee pain in the package developmentphase of a feasibility randomised controlled trial based in secondary care: a mixed-methods study. *BMJ Open*, *11*(7), p.e045242.

Nomikos, P. A., Hall, M. C., Fuller, A., Ogollah, R., Valdes, A. M., Doherty, M., Walsh, D. A., das Nair, R. & Abhishek, A. (2022). Acceptability of a nurse-led non-pharmacological complex intervention for knee pain: Nurse and patient views and experiences. PLoS ONE, 17(1), pp.e0262422

Hall, M., Fuller, A., Nomikos, P.A., Millar, B., Ogollah, R., Valdes, A., Greenhaff, P.,das Nair, R., Doherty, M., Walsh, D.A., and Abhishek, A., 2020. Protocol: East Midlands knee pain multiple randomised controlled trial cohort study: cohort establishment and feasibility study protocol. *BMJ Open*, *10*(9).

Conference Presentations

Nomikos, P.A., Fuller, A., Hall, M., Millar, B., Ogollah, R., Doherty, M., Nair, R., Walsh, D., Valdes, A., and Abhishek, A., 2020. FRI0628-HPR EVALUATING A COMPLEX PACKAGE OF CARE IN THE EAST-MIDLANDS KNEE PAIN FEASIBILITY COHORT RANDOMISED CONTROLLED TRIAL.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACL - Anterior Cruciate Ligament

ACR - American College of Rheumatology

ADLs - Activities of Daily Living

AQoL-2 - Assessment of Quality of Life II instrument

ARUK - Arthritis Research UK

BMI - Body Mass Index

BML - Bone Marrow Lesions

BRC - Biomedical Research Centre

CI - Confidence Intervals

CONSORT - Consolidated Standards of Reporting Trials

COX-2 - Cyclo-Oxygenase-2

EM – East Midlands

ES - Effect Sizes

EULAR - European League Against Rheumatism

EQ-5D-5L- European Quality of Life Five Dimension

GPs - General Practitioners

HCPC - Health and Care Professions Council

HUI - Health Utilities Index

IQR – Interquartile range

JSN - Joint Space Narrowing

K/L - Kellgren and Lawrence

KNEST - Knee Pain Screening Tool

KOOS - Knee injury and Osteoarthritis Outcome Score

LEFS - Lower Extremity Functional Scale

MACTAR - McMaster Toronto Arthritis patient preference questionnaire

MeSH - Medical Subject Heading

MFT - Muscle Function Test

MoCs - Models of Care

MOSAICS - Management of Osteoarthritis in Consultations

MRC - Medical Research Council

MRI - Magnetic Resonance Imaging

NHS - National Health Service

NICE - National Institute for Health Care Excellence

NIHBCC - National Institutes of Health Behaviour Change Consortium

NIHR - National Institute for Health Research

NSAIDs - Non-Steroidal Anti-Inflammatory Drugs

OA - Osteoarthritis

OARSI - Osteoarthritis Research Society International

OTs - Occupational Therapists

PAR - Participatory Action Research

PEDro - Physiotherapy Evidence Database

PhIT-OA - Pharmacist-initiated Intervention Trial in Osteoarthritis

PPI - Patient and Public Involvement

PRIDE - Promoting Independence in Dementia

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QMC - Queens Medical Centre

QoL - Quality of Life

QST - Quantitative Sensory Testing RCTs - Randomised Controlled Trials

REC - Research Ethics Committee

ROA - Radiographic OA

RT - Resistance Training

SF-36- 36-Item Short Form Survey

SM - Self-Management

SMART - Specific, Measurable, Achievable, Relevant, and Timely

SMD - Standardised Mean Differences

SQUIRE - Standards for Quality Improvement Reporting Excellence

SR - Systematic Review

TENS - Transcutaneous Electrical Nerve Stimulation

TEP - Technical Expert Panel

TIDieR - Template for Intervention Description and Replication

TJR - Total Joint Replacement

TKR - Total Knee Replacement

WHO - World Health Organisation

WOMAC - Western Ontario McMaster Universities Arthritis Index

1. Chapter – Introduction

1.1 Osteoarthritis (OA)

Osteoarthritis (OA) is a complex and heterogeneous disease and a variety of factors contribute to its' pathogenesis. OA is the commonest form of arthritis to affect humans and presents with pain, stiffness, disability, and affects activities of daily living (ADL) (Cross et al., 2014). OA is characterised by focal loss and destruction of the articular cartilage in conjunction with excessive growth of bone at the joint margins in an attempt to repair the damage. This results in remodelling of the subchondral bone (Schouten et al., 1992). Although OA may affect any joint type it commonly presents in knees, interphalangeal hand joints, thumb-bases, hips, and apophyseal joints in the spine (Sinusas, 2012).

This condition is mainly attributed to mechanical, biomechanical, and genetic factors with partial involvement of inflammatory components (Goldring and Otero, 2011). OA, therefore, is considered as a whole joint disease with the crucial drivers for development and progression of disease being age, gender, obesity, trauma, genetic predisposition, aberrant loading (Felson, 2009); subchondral changes, and low-grade joint inflammation, e.g., synovitis is implicated (Zhang et al., 2011).

1.2 Pathology of OA

1.2.1 Pathophysiology of OA

The major tissues responsible for OA progression are the articular cartilage and the synovial membrane. The progression of this condition occurs in three stages. Stage I involves the proteolytic breakdown of the cartilage matrix, stage II consists of the erosionof cartilage accompanied by the release of breakdown products into the synovial fluid, and stage III refers to the synovial inflammation (Martel-Pelletier, 2004). Normal adult articular cartilage consists of extracellular matrix (water, collagen, proteoglycans, calcium, salt) and chondrocytes, with type II collagen comprising the basic protein of cartilage (Goldring and

Marcu, 2009). The dysregulation of degradative enzymes (metalloproteinase, gelatinase, and aggrecanase) is responsible for cartilage destruction with degradation of macromolecules such as proteoglycans and type II collagen causing loss of cartilage volume (Goldring and Otero, 2011).

However, the origin of pain in OA is not entirely understood (Abhishek and Doherty, 2013). Most studies suggest that the cartilage is an avascular and aneural structure that does not generate pain, but peri-articular tissues such as synovium, subchondral bone, ligaments, tendons, and muscles are richly innervated by nociceptors generating pain signals (Measeet al., 2011). There are studies though that have shown vascularisation and sensory nerve growth in the cartilage of patients with knee OA (Ashraf et al., 2011, Suri et al., 2007). Two mechanisms of pain in OA have been identified: biomechanical pain which is linked with joint motion during walking, climbing stairs, and inflammatory pain which includes stiffness at rest (Chan et al., 2014).

1.2.2 Pain mechanisms in OA

Pain sensations are evoked when noxious mechanical, thermal, and chemical stimuli are applied to the joints' fibrous structures including ligaments and capsules (Schaible and Grubb, 1993). The sensory experience of pain induced by noxious stimuli is mediated by the nociceptive pain system. The nociceptive pain system not only alarms but also announces the presence of a damaging stimulus and thus, it is vital for this system not tobe disabled, to regulate the normal sensation of pain. However, when tissue damage occurs instead of the nociceptive pain system, the inflammatory pain system is activated.

The mechanisms that contribute to pain in OA are nociception, central sensitization, and peripheral sensitization (Woolf, 2004). Nociception occurs in four stages: transduction, conduction, transmission, and perception. The nociceptive message is transmitted from the periphery to the central nervous system by the primary afferent nociceptor. The latter transmits sensory information from the periphery to the dorsal horns of the spinal cord where it releases chemical transmitter substances to activate second-order pain

transmission cells. The axons of these cross over to the opposite side of the spinal cord and project for long distances to the brain stem and thalamus (Miller et al., 2015).

The process in which repetitive administration of a stimulus results in the progressive amplification of response is termed sensitization (Arendt-Nielsen et al., 2010). The definition of central sensitization is an increased response of the central nervous system that informs for pain when inputs are coming from low threshold mechanical receptors (hyperalgesia) (Latremoliere and Woolf, 2009). It also refers to alterations in the sensoryprocessing of the brain, increased temporal summation (increased response of pain in repetitive stimulation), loss of descending inhibitory mechanisms (lowering the excitationthreshold of spinal cord neurons to joint nociceptive input), and increments in the synapticexcitability (allodynia) (Lluch Girbés et al., 2013). Central sensitization is highly correlatedwith referred pain in other areas away from the affected site leading to lower pain thresholds. Hyperalgesia related to movement pain may also occur during central sensitization (Farrell et al., 2000, Mease et al., 2011).

Peripheral sensitization is a focal phenomenon and results in increased activity of peripheral nociceptors by inflammation, which involves the excitability of cellular components in the spinal cord (Im et al., 2010). Considering all these, OA pain is a complex subjective phenomenon when the aforementioned mechanisms are active and this is why its' association with structural changes varies from one individual to another (Neogi, 2013).

1.3 **Clinical Presentation of OA**

1.3.1 Pain in OA

Pain is the primary symptom in people with OA (Malfait and Schnitzer, 2013). Pain in OA is normally intermittent and worsens during and after weight-bearing activities (Bijlsma et al., 2011). The features of pain due to OA include stiffness, reduced function, joint instability, bulking, or giving way; with patients complaining also about the reduced range of movement, swelling, crepitus, and psychological distress (Hunter et al., 2008). Therefore, OA causes functional limitations (McAlindon et al., 1993) and people with OA and severe joint pain may undergo total joint replacement (TJR) (Hawker et al., 2000). However, not everyone with pain due to OA will undergo TJR (Dieppe et al., 2011).

1.4 **Diagnostic criteria of OA**

1.4.1 Clinical diagnosis of OA

Symptoms in OA precede radiographic changes by several years (Thorstensson et al., 2009). A clinical diagnosis of OA is recommended because of the poor correlation between radiographically assessed structural changes and symptoms in OA (Bedson and Croft, 2008) and may be achieved without radiographic investigations (Zhang et al., 2010a).

Table 1—1 ACR criteria for the classification of knee OA. Source (Altman et al., 1986)

Clinical	**Clinical and radiographic**	**Clinical and Laboratory**
Knee pain plus at least3 of 6: • Age > 50 years • Stiffness < than 30 minutes • Crepitus • No palpable warmth • Bony enlargement • Bony tenderness	Knee Pain plus at least 1 of 3: • Age >50 years • Stiffness < 30 minutes • Crepitus, plus osteophytes	Knee pain plus at least 5 of 9: • Age >50 years • Stiffness < 30 minutes • Crepitus • No palpable warmth • Bony enlargement • Bony tenderness • ESR[1] <40mm/hour • RF[2] <1:40 • SF[3] OA
Sensitivity: 94% Specificity: 88%	Sensitivity: 91% Specificity: 86%	Sensitivity: 92% Specificity: 75%

[1] Erythrocyte Sedimentation Route, [2] Rheumatoid Factor, [3] Synovial Fluid

Error! Reference source not found. above presents the American College of R heumatology (ACR) criteria for knee OA which is similar to the criteria developed by the National Institute for Health and Care Excellence (NICE) guideline development group. Consensus was reached regarding their definitions internationally and therefore peripheral joint OA may be diagnosed clinically if there is

- Persistent usage-related pain on one or few joints,
- Age ≥ 45 years, and
- Morning stiffness ≤ 30 minutes (Abhishek and Doherty, 2013).

Moreover, the guidelines for OA suggest not to use plain radiography for the diagnosis of this condition in the presence oftypical symptoms in the at-risk age group (NICE,

2014). The ACR criteria identify clinical OA as joint pain on most days of the previous month and report high sensitivity and moderate to high specificity for the clinical classification of knee OA (**Error! Reference source not found.**). Radiographic e xamination alone, therefore, should not be used to establish a diagnosis ofOA rather might be used to support the clinical diagnosis.

1.4.2 Radiographic Evaluation

Even though OA diagnosis is clinical, radiographic findings have been a common method to define OA in population studies (Schiphof et al., 2008). The structural severity of OA isprimarily assessed using conventional radiography with the Kellgren and Lawrence (K/L) radiographic classification tool for OA. The K/L grading method for OA provides a composite score (0-4 grade), combining osteophyte presence and joint space narrowing (JSN) with grade 2 K/L considered as the cut-off point to classify OA (definite osteophyte and possible joint space narrowing) (Schiphof et al., 2008). The description of the main features and the way they are scored radiographically using the K/L system are shown in **Error! Reference source not found.**.

Table 1—2 Kellgren and Lawrence grading scale, source (Antony, 2018)

Radiographic Grade	Classification	Description
Grade 0	Normal	Absence of radiographic features
Grade I	Doubtful	Osteophyte sprouting, doubtful JSN, bonemarrow oedema and cyst
Grade II	Mild	Visible osteophyte formation and reduction in joint space width

Grade III	Moderate	Multiple osteophytes, definite JSN, sclerosis, possible bone deformity
Grade IV	Severe	Large osteophytes, marked JSN, severe sclerosis, definite bone deformity

However, K/L grading method has its limitations; primarily, K/L does not assess the patellofemoral joint which is a frequent source of pain in knee OA, and is not adjusted forthe joint position in which the radiographs are obtained (e.g. in the knee joint semi flexed or straight). Therefore, there is also a need for standardised radiographic guidelines/protocols to assess OA progression. Previous studies underestimated the structural pathology of the condition and used restricted knee radiographic views by excluding the patellofemoral joint (Davis et al., 1992, Jordan et al., 1996) which might have led to the lack of association between knee pain and knee radiographic OA (ROA). The discordance between radiographic OA and the prevalence of knee pain is recorded in*Table 1—3*.

Table 1—3 Percentage of people with radiographic knee OA and knee pain according to the definition of knee pain

Study	Radiographic knee OA	Knee Pain %	Definition of knee pain
(McAlindon et al., 1992)	(below)	24	Positive response from both (a, b) needed
(McAlindon et al., 1993)	48	44	a) Have you ever had knee pain on most days of
(Lanyon et al., 1998)	39	53	the previous month?
(Lethbridge-Çejku et al, 1995)	29	19	(b) If so, have you experienced pain in the last year?
(Hannan et al., 2000)	15	47	Pain, swelling, morning stiffness in or around the knee on most days for one month
(Hart et al., 1991)	18	56	Pain, stiffness and swelling lasting more than a month
(Duncan et al., 2007)	68.3	74	Knee pain within the previous 12 months
(Petersson et al., 1997)	3.5	15	Pain in your knees practically daily for the last 3 months
(Odding et al., 1998)	45.4	34.9	Knee pain during the past month
(Cicuttini et al., 1996)	37.5	82.4	Ever having an episode of knee pain lasting >15 days

1.4.3 Symptom structural change discordance

Pain in OA associates with structural abnormalities, however, this association is imperfect.For instance, people with no radiographic signs may have knee pain, while people with obvious osteoarthritic changes in radiographs may not experience clinical symptoms (Guermazi et al., 2012, Kim et al., 2015). Dieppe et al. (1997) reported little or no evidence for the association between radiographic changes i.e. osteophytes and bone formation and pain in OA. The heterogeneity of the condition is further stated. Some people with severe radiographic signs of OA namely osteophytes e.g. advanced changes on plain radiographs may have mild or no pain and this can be caused due to lower pain sensitivity, lack of synovitis, or lack of bone marrow lesions (Creamer et al., 1999). Factors responsible for lower pain sensitivity are pain mechanisms that modulate sensitisation asOA progresses and comprise the disruption of the osteochondral junction by the neurovascular invasion that increases the expression of nerve growth factors (Neogi, 2017). Other factors beyond structural pathology that also contribute to pain experience include psychological factors.

Despite this general discrepancy, a positive association between knee pain severity and knee radiographic OA severity is reported (Davis et al., 1992, Duncan et al., 2007, Felsonet al., 1987, Lawrence et al., 1966, Neogi et al., 2009). Duncan et al. (2007) has found astrong association between radiographic OA severity with pain severity and pain persistence odds ratio [OR 3.7, confidence interval (95% CI) and [OR 2.8, (95% CI)]. TheChingford study (Hart et al., 1999) has found a significant association between knee painand knee osteophytes [OR 2.38, (95% CI), (1.29-4.39)] and this relationship has also been confirmed by other studies (Duncan et al., 2007, Spector et al., 1993). An association between the structural markers of OA and the symptoms of the condition, therefore, mayexist.

A significant factor that played a major role regarding the differences in these studies is the varied population included and the severity of pain. The latter is a subjective experience which is unique to each person. A factor (pain) that is causally associated with the outcome (OA) is not a strong predictor of response on its own, as residual confounding may dilute the association

between radiographic knee pain and radiographic knee OA.

Other potential abnormalities not visual on radiographs but visual on other imaging modalities e.g. Magnetic Resonance Imaging (MRI), such as subchondral bone changes (sclerosis, cysts, bone remodeling), synovitis and effusion are associated with knee pain (Sowers et al., 2011). A systematic review reported moderate levels of evidence for the association between Bone Marrow Lesions (BML) and effusion/synovitis with knee OA pain: [OR 2-5, (95% CI), (2.4-10.5)] and [OR 2.6-10, (99% CI), (1.13-149)] respectively (Yusuf et al., 2011). BMLs often referred to as bone marrow oedemas/bone bruises are identified as regions of hyper-intense marrow signal in MRIs and are associated with microscopic bone damage (Alliston et al., 2018). Ultrasound-detected synovial changes are associated with early knee pain : [OR 3.17, (95% CI), (1.17-8.53)] and established knee pain : [OR 4.97, (95% CI), (1.66-14.86)] (Sarmanova et al., 2017).

1.5 **Knee pain and knee OA**

Pain is a marker for incidence of knee OA and the primary reason for healthcare consultation (Chan et al., 2014, Hochberg, 1996). Knee pain is common in the elderly andthe young. One in four people over the age of 55 report a painful episode in the past year(Peat et al., 2001). However, different studies use different definitions of knee pain. For example, in many studies, knee pain is defined according to whether individuals report pain, aching, or stiffness on most days of the previous month (Hernández-Molina et al., 2008, O'reilly et al., 1996). The Framingham study defined knee pain as having persistentpain that lasts at least a month in or around the knee, including the back of the knee (McAlindon et al., 1999).

1.5.1 The character of knee pain

It is important to understand how knee pain alters over time as the condition progresses,its' most distressing features, how pain is being perceived by the individuals thatexperience this condition, and its impact on patients' quality of life (Hawker et al., 2008). Hawker et al. (2008) used the Patient-Generated Index to capture and identify the various types and characteristics of OA pain (*Table 1—4*)

Table 1—4 Identification of pain descriptors. Source: (Hawker et al., 2008)

Category	Descriptors
Pain intensity	Intense, severe, quite, bad, mild Moderate, less severe, worse, better
Severe pain	Sharp, stabbing, shooting, knife-like,needle-like, brings tears to eyes
Frequency and duration	Every-day, consistent in morning constant, gradual, there all the time
Predictability	Unsure when pain will come, unsure, pain comes out of nowhere
Night pain	Sharp pain comes on at night, difficult to sleep, that's when it really aches
Neuropathic pain	Burning, pins and needles, numbness
Effect on mood	Paralyzing, terrorizing, want to scream

OA-related pain was described according to intensity, severity, frequency and duration, predictability, night pain, neuropathic pain, and effect on mood. Patients reported that lifestyle changes have been made because of pain, and that knee pain progressively got worse over time. The study concludes that intensive and unpredictable knee pain was found to have a great impact on people's quality of life. Participants identified that the more intense, unpredictable, and emotionally draining pain significantly resulted in socialand recreational avoidance.

1.5.2 Risk factors for knee OA and knee pain

The risk factors for OA have been categorized into systemic and local risk factors (Felson, 1988, Felson et al., 1997). While systemic factors act by increasing the susceptibility of the joint to OA and

by impairing the repair process of the damaged tissue, local factors are more biomechanical in nature (Litwic et al., 2013). These factors are not discrete from each other, and they interact together to determine the overall risk of OA (Arden and Nevitt, 2006). However, the risk factors for the development of knee OA differ from thosefor the progression of the condition (Doherty, 2001). Similarly, because knee pain may not only occur due to structural peripheral changes of OA, and may be driven by local or central neuroplasticity the risk factors for OA do not always correlate with those for kneepain (Miranda et al., 2002). *Table 1—5* Indicates the risk factors for the development andprogression of knee OA as described by Doherty (2001).

Table 1—5 Risk factors for development and progression of knee OA. Source:(Doherty, 2001).

Development	Progression
Heredity	Low bone density
Ageing	Low intake vitamins C and D
Female sex	Instability
Trauma / meniscectomy / ligament rupture	Varus / valgus malalignment
Knee laxity Occupation / sports • Professional soccer • Repetitive knee bending	Chondrocalcinosis / Calcium Knee effusion
Quadriceps weakness	Indomethacin
High bone densityHand OA Obesity	Obesity

Increased Body Mass Index (BMI) is a strong modifiable factor for knee pain and knee OA(Blagojevic et al., 2010, Ingham et al., 2011). Age, previous knee injury, occupational risk, and knee straining work are deemed to be important risk factors for the incidence ofpersistent knee pain (Andersen et al., 1999, Fernandes et al., 2018, Ingham et al., 2011,Miranda et al., 2002). Keefe et al. (2000) acknowledged that women with OA experiencemore pain compared to men and this may be due to pain catastrophizing behaviour in OA pain. Age, knee pain, and morning stiffness comprise the most important independent predictors of disability (Odding et al., 1998). Strength, mental health, self-efficacy, and social support, work as protective factors against the poor functional outcome of knee OA (Sharma et al., 2003a).

1.5.3 Local mechanical risk factors

The local biomechanical factors have been documented by Felson et al. (2000). Obesity (BMI > 30kg/m2) is a significant risk factor that is associated with the development and progression of knee OA (Grotle et al., 2008), pooled OR 2.63, (95%CI), (2.28 – 3.05) (Blagojevic et al., 2010). History of previous knee injury is also a risk factor for the development of knee OA with overall OR 4.20 (95% CI), (3.11 – 5.66) (Muthuri et al., 2011). Young adults may develop knee OA as a consequence of knee injury. Roos (2005)showed that 51% of women and 41% of men who sustained anterior cruciate ligament (ACL) injury in soccer, had knee OA after twelve and fourteen years respectively. Specific activities related to excessive kneeling, squatting, climbing steps, standing more than twohours, and lifting are associated with the development of knee OA (Coggon et al., 2000, Dawson et al., 2003, Lau et al., 2000, Manninen et al., 2002, Yoshimura et al., 2004) Knee alignment is another risk factor for the development of knee OA with varus or valgus deformities comprising the major reason for increments in the aberrant loading of the kneejoint. OA knees with valgus and varus deformities increased the risk of progression in thebiomechanically stressed joint and decreased the risk of progression in the unloaded compartment (Sharma et al., 2001). Muscle strength studies agreed that quadriceps' weakness is related to knee OA and knee pain, but to which extent this is an independentrisk factor is not known (Murray et al., 1980).

1.5.4 Systemic risk factors

Knee OA is age and gender-related. Women over the age of 50 years are more likely tohave the condition compared to men pooled OR 1.8, (95% CI), (1.1 – 3.1) (Felson et al., 1997). The susceptibility of women to more severe knee OA is attributed to the postmenopausal decline in sex hormone, which is protective against OA (Sowers et al., 2006). Instead of a mechanical risk factor, obesity is also a systemic metabolic risk factorfor knee OA. High bone mineral density is associated with an increased prevalence of OA.However, once OA has established bone mineral density was found to be protective against this condition (Zhang et al., 2000). Dietary habits e.g. low intake and low serum levels ofvitamin D comprised an increased risk factor regarding the progression of knee OA (McAlindon et al., 1996). Finally, clear evidence of genetic predisposition of knee OA for women is reported (Spector et al., 1996).

1.6 **Epidemiology of knee pain**

1.6.1 Prevalence of knee pain

In the UK, the annual prevalence of knee pain for older adults ranges between 10% and 52.2% (*Table 1—6*). A postal survey study found that knee pain is equally common in bothsexes until the age of 60 years (McAlindon et al., 1992). After that age, the prevalence ofknee pain rose significantly and became more prevalent in women than in men. However,as previously reported, knee pain studies used different definitions of knee pain to capturethe overall prevalence (Table *1—3*). For example, O'reilly et al. (1996) compared the threequestions that enquired about knee pain and were used in previous knee pain survey studies and highlighted that knee pain estimates are influenced by changes in the questionnaire's content. The study, which captured the highest rate 46.8% [95% (CI) 45.6%, 48%] in the annual prevalence of knee pain (77% response rate) for people aged55 years and over, used the Knee Pain Screening Tool (KNEST) (Jinks et al., 2003). The Nottingham Knee Pain and Health in the Community study (Fernandes et al., 2018) reports the prevalence of knee pain in ex-footballers at 52.2% and in the general population 26.9%.

Table 1—6 Prevalence of knee pain in the UK in survey studies

Prevalence (%)	Author	Population	Year	Design	Age-range (years)	Response rate (%)
25	McAlindon	GP registered community dwelling adults	1992	Postal-survey	55-85	80.6
19.3,25.3,28.3	O'Reilly	GP registered community dwelling adults	1996	Postal-survey	40-79	81.9
19	Urwin	GP registered	1998	Postal-survey	45-75	78.5
10	Badley	Joint problems	1992	Postal-survey	16-85	87
46.8	Jinks	GP registered	2004	Cross-sectional survey	50-75	77
26.9		General population		Cross-sectional survey	47.3-73.3	24
52.2		Ex-football players				

1.6.2 Incidence of knee pain

Few studies report the incidence of knee pain. Jinks et al. (2008) stated that among 2,059people aged ≥ 50 years with no knee pain at baseline, 24% complained about knee pain after 3 years. The cumulative incidence proportion increased over time. Ingham et al. (2011) determined the cumulative incidence of knee pain following a 12- year follow-up period. The study has found that in 2,156 people aged ≥ 40 years with no knee pain at baseline, the cumulative incidence proportion after 12 years was 34.4% (742) equal for both men (32%) and women (35%). The incidence rate of knee pain in person-years wasfound 32/1000 in this study. Bagge et al. (1992) report on the

incidence of joint complaints referring to pain, stiffness,or swelling in a 5-year follow-up period for people aged ≥ 70 years old. Women had a higher rate of joint complaints (15%) compared to men (3%). The study has found that the most common site of complaint was the knee for both sexes, but their population wasnot representative and their results refer only to people aged 70-75 years old. Miranda et al. (2002) included 2,122 workers that were free of knee pain at baseline and reported the incidence rate of knee pain after a year follow-up at 10%.

1.6.3 Impact on the individual and healthcare system

Symptomatic knee OA is associated with functional limitations such as walking over moderate distances e.g. three city blocks, and climbing stairs (Neogi, 2013). People withpainful knee OA may also have slower walking speed compared to those without knee OA(Al-Zahrani and Bakheit, 2002). Knee pain severity is highly associated with restricted mobility outside the home. However, improving the environment in which people with knee pain live may reduce the disability of knee pain and increase the participation levels (e.g.easy access to public transportation) (Wilkie et al., 2007)

Approximately 8.5 million people in the UK have OA joint-related pain (Conaghan et al., 2008). The Royal College of General Practitioners (GPs) reports that over 1 million individuals consult their GP with OA symptoms (Chen et al., 2012). Jordan et al. (2006) stated that the incidence of a new GP consultation for adults with knee pain aged over 50years is 10% each year. Among adults aged 55 and over, Peat et al. (2001) stated that 1.5% of the population across Europe consult their GP with severe and disabling knee painattributed to OA in the course of a year.

This condition results in 135,000 TJRs each year, and the total costs for National Health Service (NHS) are estimated to be £5.2 billion annually, with more than 6 million people reporting knee pain due to OA either bilaterally or unilaterally (Patel et al., 2009). More evidence that is recent suggests that OA is the main indicator for surgery in 97% of TotalKnee Replacement (TKR) patients. This is supported by the National Joint Registry which recorded 103,126 TKRs in 2014, a number that increased by 11,423 (12.4%) since 2013(Registry, 2015). Considering the projected aging of the population, the rising in obesity,and the age differences within the UK, the predicted number of

TKRs in 2035 is estimatedto be 118,666 (Culliford et al., 2015).

1.7 **A holistic approach to OA assessment and management**

1.7.1 Holistic assessment of person with OA

NICE guidelines (NICE, 2014) have recommended a holistic approach for the managementof OA (Figure 1—1), considering the needs of individuals, their social situation, psychological factors (e.g. anxiety or depression), quality of sleep, and their ability to copewith their ADL.

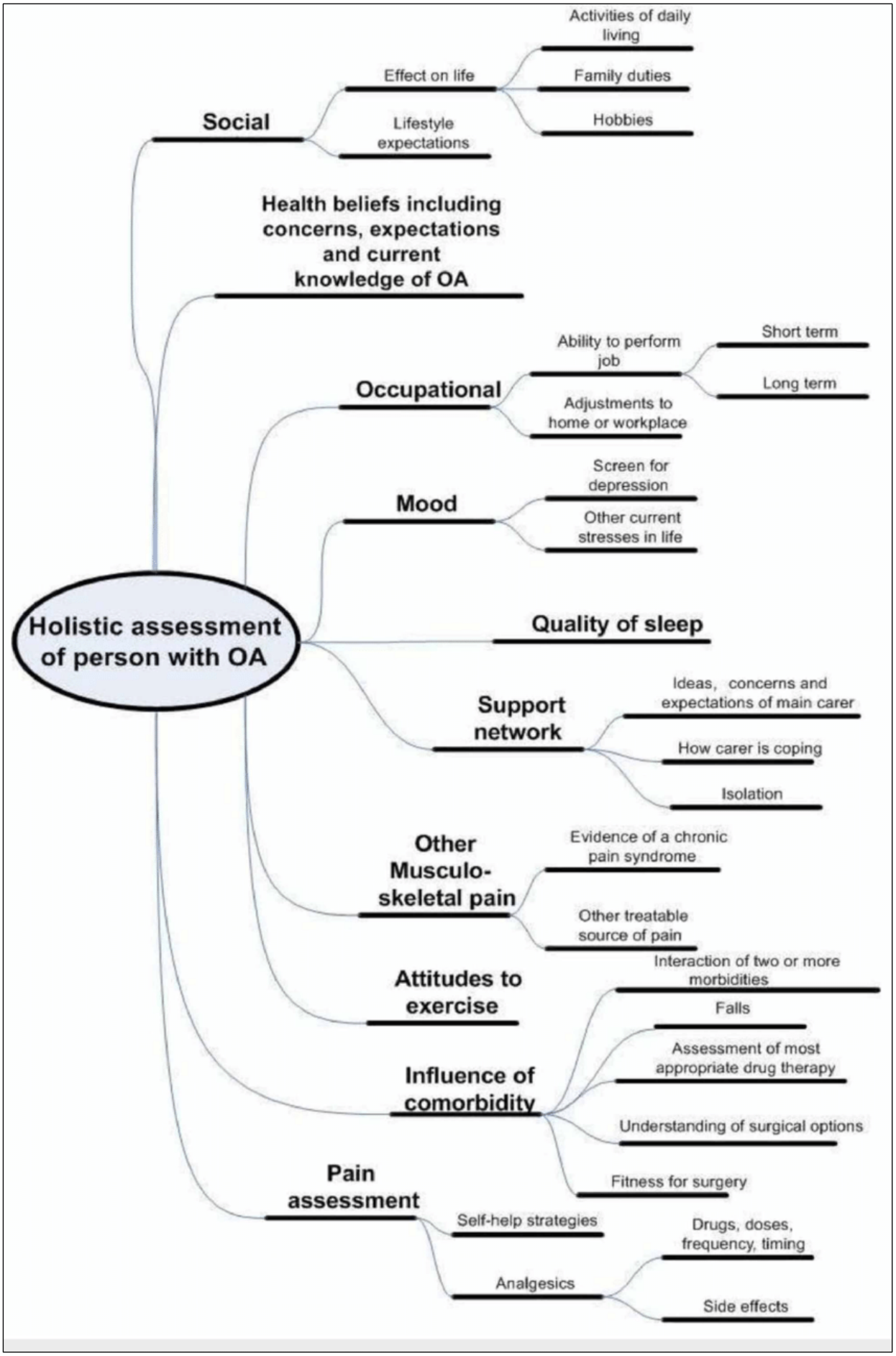


Figure 1—1 Holistic assessment of person with OA. Source: (NICE, 2014)

For this reason, NICE suggests that healthcare professionals should assess OA's impact on the individual's function, mood, quality of life, occupation, relationship, and leisure activities. A personalised treatment plan should be agreed upon in collaboration with the individual with OA taking account of any comorbidities.

OA people may normalise their condition by reporting that OA is part of ageing, while others may alter their life trying to alleviate pain. In addition, they may not follow their physicians' advice when they receive only pharmacological recommendations as many such medicines have low efficacy for OA pain or cause side-effects (Maniar et al., 2018); or when self-management strategies are not provided (Gignac et al., 2006).

It is important to examine and address patient perception in OA. Pain in OA is associated with modifiable factors namely personal factors and an important characteristic of those factors that influences this association is perceptions of patients about the disease (Bijsterbosch et al., 2009, Hill et al., 2007). A way to address patients' perceived perception about OA is by changing negative illness perception through education and provide the patient with self-management strategies. Results from previous studies suggest that illness perceptions in patients with OA might influence health behaviour and symptoms (Botha-Scheepers et al., 2006, Keefe et al., 2000). Of these catastrophizing is an important feature to address. Catastrophising is defined as "an individual's tendency to focus on and exaggerate the threat value of painful stimuli and negatively evaluate one'sability to deal with pain'' (Keefe et al., 2000) p326. Catastrophising behaviours by individuals with OA correlated with symptoms (Keefe et al., 2000). Interestingly, the more serious and symptomatic participants' thoughts have been about their condition, the less positive they were about outcomes of OA management and, as a result, the less they would adhere to treatment (Hampson et al., 1994).

1.8 **Management of OA**

1.8.1 Surgical and non-surgical Interventions

TKR surgery is an effective treatment for end stage knee OA (Carr et al., 2012). Research supports the effectiveness of the non-surgical interventions for the management of knee OA with moderate evidence (McAlindon et al., 2014). TKR also has lower success rates than total hip replacements and may cause serious adverse effects with two of the most common reported being deep vein thrombosis and stiffness requiring brisement force. Clinically relevant improvements for pain and physical function are reported for both surgical and non-surgical interventions, however the ratio of adverse events in TKR vs non-surgical treatment is 8:1 and it is expensive (Skou et al., 2015). Therefore, there is a need to improve non-surgical interventions to either defer or negate the need for surgery.

1.8.2 National and International Guidelines

Systematically developed national and international guidelines have been published to assist healthcare professionals in their decision-making for knee OA management (*Table 1—7*).

Table 1—7 International and National guidelines for the management of OA

Author (Year)	Organisation	Joint areas covered	Scope and Purpose
Hochberg et al. (2012)	ACR[1]	Persons with hand, hip, and knee OA	Update the ACR 2000 recommendations
Pendleton et al. (2000)	EULAR	Persons with knee OA	Five stages to generate recommendations
Jordan et al. (2003)	EULAR[2]	Persons with knee OA	Update EULAR (2000) recommendations
Members et al. (2001)	Philadelphia Panel Evidence	Persons with knee OA and knee pain	Form an expert panel to generate recommendations
Vogels et al. (2001)	Dutch-KNGF[3] forphysical therapy	Persons with hip or knee OA	Targeting physical therapists – review of the evidence
Zhang et al. (2007)	Osteoarthritis Research Society International (OARSI)-Part I	Persons with hip and knee OA	Critical appraisal of existing treatment guidelines and a systematic review
Zhang et al. (2008)	OARSI[4]-Part II	Persons with hip and knee OA	Delphi exercise to generate consensus Recommendations
Zhang et al. (2010b)	OARSI-Part-III	Persons with hip and knee OA	Update evidence for available therapies

[1] American College Rheumatology

[2] European League against Rheumatism

[3] Royal Dutch Society for Physical Therapy (translation in English)

[4] Osteoarthritis Research Society International

Systematic reviews, Delphi rounds, and technical expert panel (TEP) opinions have been the methodologies used to identify the core treatment modalities. The common key message suggested by these guidelines to achieve the optimal management for patients with knee OA is to deliver a person-based approach using a combination of pharmacological and non-pharmacological modalities. Shekelle et al. (1999) recommend a multidisciplinary team to be involved in the guideline development group, and that group is representative of all stakeholders whose profession is under consideration. European League Against Rheumatism (EULAR) included rheumatologists and

orthopaedic surgeonsin their steering group committee to develop the guidelines, while American College Rheumatology (ACR) extended their TEP as their past guidelines included only a small steering group.

1.8.3 National Institute for Health Care Excellence (NICE)

NICE (2014) recommends core, adjunctive non-pharmacological, and pharmacological treatments for OA. The core treatments comprise three components namely exercise (local muscle strengthening, aerobic fitness), advice (to exercise irrespective of age, comorbidity, pain severity, or disability), and weight loss if overweight or obese.

The adjunctive non-pharmacological components include self-management strategies, suitable footwear for pain and stability (insoles), transcutaneous electrical nerve stimulation (TENS), local heat or cold applications, and assistive devices (walking aids orsticks) if biomechanical joint pain is present.

The adjunctive pharmacological treatments that target optimise drug interventions include paracetamol and topical non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief that should be offered before oral NSAIDs and cyclo-oxygenase-2 (COX-2) inhibitors or opioids. Opioid analgesics should be offered if paracetamol and topical NSAIDs are inefficient for pain relief or replace them with oral NSAIDs or COX 2 inhibitors at the lowesteffective dose for the shortest period of time. Finally, intra-articular steroid injections should be offered when pain is moderate to severe.

Until the publication of NICE (2014) guidelines regarding the management of OA, core treatments for OA were underused and patients and doctors mainly emphasised in systemic analgesics alone (Porcheret et al., 2007) and ignored OA symptoms (Gignac et al., 2006). In addition elements such as frequency, intensity, type, and duration of exercise are not reported even within the most recent published guidelines (NICE, 2014) and the type of healthcare professional who can manage and deliver treatment to patientswith knee OA is not mentioned.

1.9 **Models of Care (MoCs) in OA**

1.9.1 Overview

Multiple efforts have been made to develop treatment protocols for the management of knee OA based on research evidence and guidelines in multiple countries. Programmes have been developed to bridge the gap between OA recommendations and practice (Atukorala et al., 2016, Dziedzic et al., 2014, Eyles et al., 2014, Hay et al., 2006, Knoop et al., 2013, Skou and Roos, 2017, Thorstensson et al., 2015). *Table 1—8* introduces andcriticizes paradigms of such programmes and provides details on the target population, eligibility criteria, duration, intervention, outcome measures, etc. Studies have varied in terms of the implementation, content, and duration of treatment; the intensity of exercisehas varied and programmes' duration has ranged from 18 weeks to 12 months. In addition, different types of healthcare professionals were involved in the management of knee OA.

Table 1—8 Description of models of care across the spectrum of OA

Brief Name	OACCP [α]	BOA[β]	AMSOA[δ]	OAHWFL [x]	MOSAICS[ο]	EPRCP"
Design (country)	Observational-cohort (Australia)	Evidence-based (Sweden)	Single-blind RCT (Amsterdam)	Community (Australia)	Mixed-methods cluster RCT (UK)	Pragmatic multicentre RCT (UK)
Participants	Knee/hip OA	Knee/hip OA	Knee/hip OA	Knee/hip OA	Knee/hip/hand /wrist/ foot/ankle OA	Knee pain
Eligibility criteria	GP diagnosis OA (clinical)	GP diagnosis OA (clinical)	ACR criteria for OA	ACR criteria for OA	GP diagnosis OA (clinical)	Knee pain presenting to a GP
Duration*	6	12	9	4	12	12
Outcome measures	WOMAC[1], KOOS[2], VAS[3], 6MWT[4], DASS-21[5]	Patient reported compliance and satisfaction	WOMAC, NRS, TUG[6],SF-36[7], medication use	WOMAC, KOOS pain subscale	Quality of OA care-electronic template	WOMAC pain subscale, GAF[8], pain severity, ASES[9], HADS[10]
Sample size (n)	559	20,200	159	1,383	1,960	325
No of Groups	-	-	2	-	2	2
Targeted interventions	Individualised exercise programme focusing on muscle strength, and increase in physical activity levels	Group sessions spread over two theoretical sessions: education about OA, exercise and weight loss information	Both groups received exercise for 12 weeks. Group sessions consisted of exercise in three phases; (2 sessions x 60 minutes weekly) and home exercise for 5 days weekly.	Web-based individualised programme with three phases (motivational weight loss, consolidation weight loss, weight maintenance	Enhanced GP consultation and provision of a nurse-led clinic supported by an OA guidebook. Control group received usual care	Community physiotherapy (3-6 sessions x 20 min / 10 weeks), Pharmacy review (targeting analgesia), and a control group (leaflet information and telephone call by nurse)

Table 1—8 Continued

Healthcare Professionals involved	Physiotherapist, rheumatologist, nurse, dietician, psychologist, occupational therapist	Physiotherapist, occupational therapist, expert patients	Physiotherapist	GP	GP, nurse	GP, nurse, pharmacist, physiotherapist
Time points✞	26	13 and 52	6, 12, and 38	6 and 18	26	13, 26, and 52
Results	Knee OA participants most likely to respond compared with those with hip OA [OR 1.92, (95% CI) (1.02, 3.62)].	97% completed the theoretical part, and 83% optional exercise. After week 13, 62% reported daily use of programme, 91% weekly use. After 52 weeks, 83% rated the intervention as good, 37% reported daily use and 72% weekly use. Dropout rate was 28%.	Clinically significant improvement in knee pain for both groups, sustained 6 months after. 78% of the participants adhered to exercise programme	748 achieved a weight loss ≥ 7.5%, while 332 were between 5 and 7.5%. 1/3 achieved >10% weight loss and this was associated with greater improvement in KOOS pain subscale.	Reduction in x-ray requests (25-15%), [OR 0.45 (95%CI), (0.12 – 1.72)] and increase in paracetamol prescription for the intervention group	Improvement in WOMAC pain scores for physiotherapy and pharmacy arms at week 13. Improvements not sustained at weeks 26 and 52. Use of NSAIDs was decreased in physiotherapy and pharmacy group compared with control.
Concerns/ Limitations	Did not include a control group. Patient adherence is not reported	Patients informed the content of sessions. Patient – centred outcome measures collected but not reported	Patient adherence may optimise treatment sustainability	Web-based intervention may improve knee pain. Patient and provider adherence not reported and study unable to show the sustainability	Only 29% of patients in the intervention arm reported a consultation with a nurse. No statistically significant differences between intervention and control	Lack of reporting of patient adherence that might have influenced the long-term clinical benefit.

[1] Western Ontario and McMaster Universities Arthritis Index, [2] Knee Injury and Osteoarthritis Outcome Score, [3] Visual Analogue Scale, [4] 6-minute walk test, [5] Depression Anxiety and Stress Scales, [6] Time up and Go, [7] Short form, [8] Global Assessment of Functioning, [9] American Shoulder and Elbow Surgeons questionnaire, [10] Hospital Anxiety Depression Scale, * Months, ✞ Weeks, ᵅ OA Chronic Care Program Model of Care, ᵝ Better Management of patients with OA, ᵟ Models of healthcare delivery for OA, ˣ OA Healthy Weight for Life, ᵒ Model OA Consultation, "Community Physiotherapy and pharmacy review

Mainly, studies involved trained physiotherapists to deliver the intervention (Knoop et al.,2013, Skou and Roos, 2017, Thorstensson et al., 2015), others involved trained doctors and nurses (Jordan et al., 2017) and others used patients with the condition (Skou and Roos, 2017, Thorstensson et al., 2015). The MOSAICS study (Jordan et al., 2017) was a two-arm cluster RCT that developed a model intervention for OA informed by NICE guidelines, and based on the behavioural change wheel (Michie et al., 2011). However, the MOSAICS study did not report the effectiveness of model OA intervention rather they reported a recorded achievement (yes / no) of the specific quality indicators (assessment, core interventions, non-pharmacological and pharmacological interventions) of primary care OA and this is a significant limitation.

The targeted patient populations (knee, hip, hand, wrist, foot, and ankle OA, joint pain) used in the studies varied, and different definitions of knee pain for the inclusion/exclusioncriteria have been used. Even though studies have followed national and international guidelines for the management of knee OA, not all of them considered weight loss as a core treatment for the management of knee OA. One study (Eyles et al., 2014) reported that weight loss may not be a predictor of response for a better outcome in the management of knee pain.

Additionally, it seems that most of the studies considered different implementation theories based on behavioural change models (Gallacher et al., 2011, Grol and Wensing, 2004, Michie et al., 2011, Wagner, 1998) for the development of their intervention. In anycase, the use of a behavioural change theory is of significant importance for thedevelopment and implementation of complex interventions (Allen et al., 2016b). Reviewing the different models of care of OA from Table 1—8, it is apparent that there isa need to systematically evaluate, over time, the outcomes and impacts of the non-pharmacological OA management programs to support the spread of effective models of care for OA. Finally, there are lessons learned from reviewing these models and are recorded below:

1. Support from all the relevant stakeholders whose profession is under consideration (healthcare professional groups) is necessary

2. Consistent delivery of the programmes should be provided, taking into consideration any local resources and structures

3. Consistent evaluation and use of outcome data collection

4. Patient adherence with the intervention should be reported

5. Fidelity of delivery is an important aspect and should be considered

1.10 **Long-term management of knee pain**

1.10.1 Who should be managing?

There are many barriers for doctors to manage knee pain due to OA such as time constraints and core non-pharmacological treatments are under-utilised (Egerton et al., 2018, Porcheret et al., 2007). Enhanced GP consultations based on an OA guidebook followed by referral to a practice nurse-led clinic for OA and provision of written informationon OA did not improve many quality indicators for knee OA care in the recent MOSAICS study (Jordan et al., 2017). However, the extent to which the nurse-led clinic influenced the outcome for the management of OA is unspecified as only 21% of patients with clinicalOA attended the practice nurse clinic.

Hay et al. (2006) examined physiotherapists and pharmacist-led management of symptomatic knee OA. They compared the effectiveness of enhanced pharmacy review (targeting analgesia), community physiotherapy (3-6 sessions x 20 min / 10 weeks), anda control group (information and advice leaflet reinforced by a telephone call from a nurse). Physiotherapy and pharmacy interventions resulted in improved WOMAC pain scores at 3months but this was not sustained at 6 months [mean difference (1.15 – 0.14) for physiotherapy], and [(1.18 – 0.41) for

pharmacy group].

Nurse-led models for chronic conditions seem to be effective when compared to physician-model in terms of implementation, adherence, patient satisfaction, and individualisation. Trained nurses delivered the intervention following protocols and guidelines, achieved similar outcomes (sometimes better) compared to physicians, and provided recommendations for the management of pharmacological and non-pharmacological carein patients with type II diabetes, heart failure, cardiovascular disease, and different coursediseases (Denver et al., 2003, Martínez-González et al., 2015, Martínez-González et al., 2014, Sisk et al., 2006)

Therefore, we hypothesize that a nurse-led complex package of care where a trained nurse is the key contact with patients and commences the management of the core pharmacological and non-pharmacological components by educating them about their condition, teaching them aerobic exercises and building a long-term therapeutic relationship, is likely to be effective in the management of knee pain due to OA.

1.11 **Nurse-led models of care for chronic conditions**

1.11.1 The nurse-led approach is effective in healthcare

Numerous studies have shown that nurses are appropriate health care professionals to deliver care in chronic health conditions compared to physicians when following guidelines (Denver et al., 2003, Martínez-González et al., 2015, Welch et al., 2010). More precisely Denver et al. (2003) showed that nurses were able to deliver pharmacological and non- pharmacological advice based on NICE guidelines to their patients for antihypertension management.

According to World Health Organisation (WHO) (Organization, 2007), task shifting is a process in which specific tasks where appropriate, are moved from highly qualified healthcare professionals to less trained healthcare professionals with fewer qualifications to increase the efficacy of human resources in health. A systematic review explored the evidence of physician-nurse task shifting in primary care for the management of different course diseases (heart, lung, metabolic, digestive, skin, infectious) (Martínez-González etal., 2015). Although nurses received training on how to deliver the treatment (Martínez- González et al., 2015) a lack of information exists regarding the description of nurses' competency and their training aspects within studies (Sisk et al., 2006,

Denver et al., 2003). Nevertheless, the systematic review concluded that nurses can achieve outcomes that at least are equal to physicians for the management of a chronic disease. Not only this, nurses were found to achieve better outcomes on the prevention of heart disease, dyspepsia, and on reducing the risk of cardiovascular disease in diabetic patients (Martínez-González et al., 2015).

A Cochrane review evaluated the effects of nurse-led titration of beta-blockers, angiotensin receptors blockers, and angiotensin-converting enzyme inhibitors targeting heart failure patients (Driscoll et al., 2015). The review found that nurses could deliver first-line treatments in heart failure by optimising medication and managing titration for patients better when compared with the primary physicians who seemed to be reluctant to up- titrate medication (Driscoll et al., 2015). Likewise, the nurse facilitated patient education and self-management of heart failure at home, and this improved patients' outcomes. Thenurse-led titration group experienced fewer deaths and hospital admissions compared to the usual care group (RR 0.60, 95% CI, 0.46 to 0.77). Following the results of previous RCTs for the management of heart failure and type II diabetes (Denver et al., 2003, Sisk et al., 2006), nurses were the first point of contact with patients, educated them about heart failure and systolic dysfunction, discussed physical activity levels, recommended alternations to patients' medication, and signpostedpatients to the appropriate social services. It is noteworthy to report that in both studies (Denver et al., 2003, Sisk et al., 2006) nurses followed a protocol based on national clinicalevidence-based guidelines. Additionally, nurses assessed patients' adherence to medication via a telephone call and discussed the adverse effects of their current medication. Overall, studies have found that a nurse-led approach is more effective in the management of hypertension, may improve functioning and lower hospitalisations.

1.11.2 Why a nurse-led care model?

Martínez-González et al. (2014) have found significantly improved results on the effect ofnurse-led care models on patient satisfaction. Patients with minor illnesses were more satisfied with consultations by the nurses compared to doctors (mean score of satisfaction78.6/100 for nurses versus 76.4/100 for doctors), and the former spent more time with the patients (Shum et al.,

2000). Nurses have some positive qualities to provide self- management (Dziedzic et al., 2013). Particularly nurses listen to patients, improve their motivation, modify behaviour, break the tasks down, involve carer, and engage and manage people with chronic disease in the long-term (Macdonald et al., 2008). Finally, nurse-led consultations appeared to be cheaper than GP consultations in treating commonconditions (Dierick-van Daele et al., 2010).

1.12 **Developing and Evaluating Complex Interventions**

1.12.1 What is a complex intervention?

A complex intervention has several active elements that work together to provide treatment effect. These elements refer to individual interventions, their parameters (e.g. timing and frequency), and their organisation (e.g. types of healthcare professionals, location, and setting) (Craig et al., 2008). Complex interventions have non-linear causal pathways compared to simple interventions that have simple linear pathways linking intervention to the outcome. A complex intervention may also be seen as a set of simple interventions by unpacking the individual components and examining the effects of its' single parts (Petticrew, 2011). However, this might not be feasible to explore, as there would be an interaction between the different elements so the effect size will not be the true effect size of the whole intervention. Table 1—9 outlines the differences between simple and complex interventions.

Table 1—9 Differences between simple and complex interventions (Campbell et al., 2000)

Simple Intervention	**Complex Intervention**
Requires simple perspective	Requires complex perspective
Single components	Multiple components
No interaction among the components	Components interact together
Focuses on individual alone	Focuses on outcomes at different levels
Non-simplified	May be simplified
Assesses the outcomes	Explores how the elements work together
Search for efficacy	Search for synergies
Simple methodologies and analyses	Different methodologies and analyses may be useful for different types of users/researchers

A good theoretical understanding of how the intervention causes change is important. A complex intervention can be strengthen when the range of the effects, the variation of the effect among the recipients, and the reasons for variation are identified. Once this has been achieved, emphasis should be given to refine and fine-tune the intervention (Craig et al., 2008). However, to apply the intervention among different groups and settings, we need to understand the causal mechanisms of the intervention, by identifying the active ingredients and their inter-relationship. Fine-tuning the intervention will provide the opportunity to tailor the intervention according to specific needs and circumstances (Campbell et al., 2000). Medical Research Council (MRC) guidelines for developing and evaluating complex interventions, mentioned the steps to be undertaken to develop and evaluate complex interventions for RCTs (*Figure 1—2*).

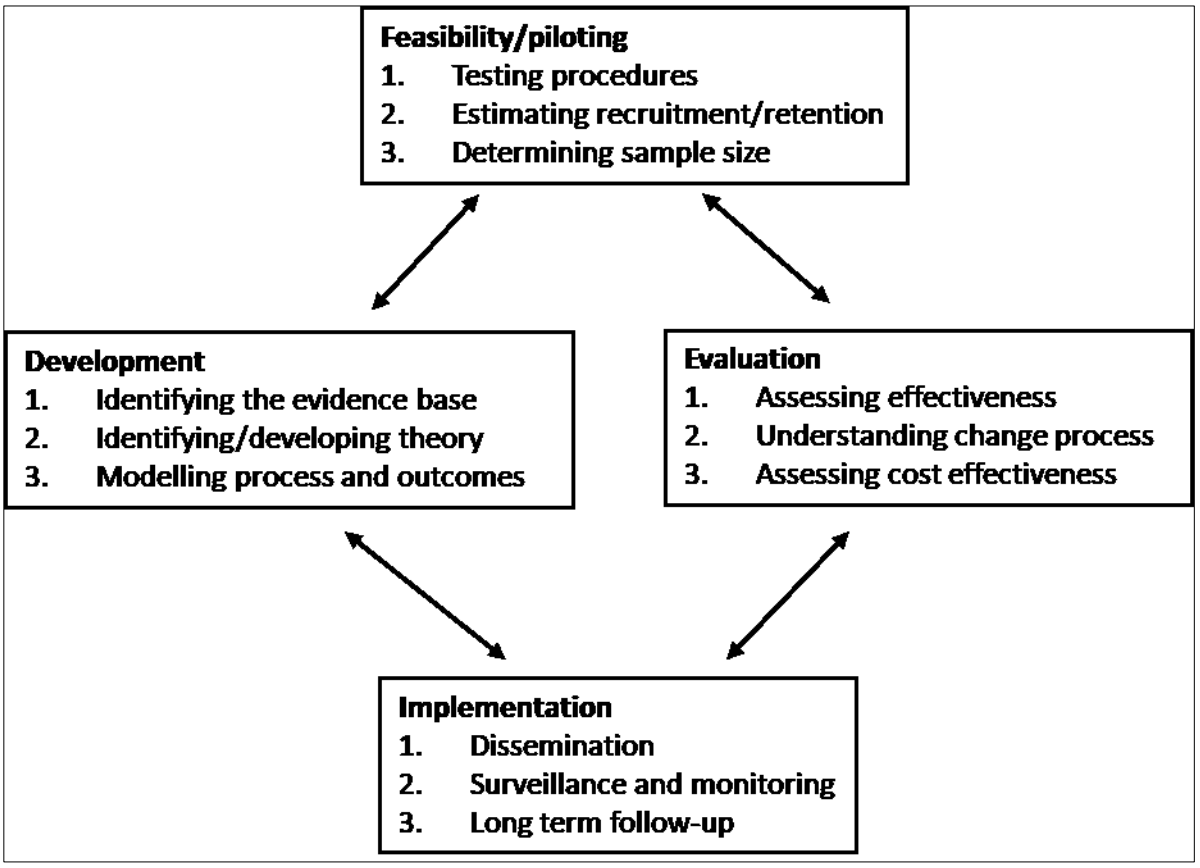


Figure 1—2 Key elements of the development and evaluation process (Craig et al., 2008)

1.12.2 Development-Evaluation-Implementation process

Before the definition and the development of any complex intervention, main stages, keyfunctions, and activities at each stage have to be considered (Craig et al., 2008). The arrows in figure 1-2 indicate the interaction among these stages. These do not follow a linear or cyclical sequence. Before progressing to research evaluation, we first need to develop the intervention. This includes:

- Evidence base—identify the most relevant existing evidence using a systematicreview

- Theory—The best choice of intervention ensured by exploring relevant theory (interviews with the stakeholders)

- Modelling—Components of intervention identified and their inter-relationship (useful to determine the design of the intervention and evaluation).

However, a flexible approach should be used when following these recommendations as some aspects of the guidelines may not be relevant to some interventions and/contexts, and not all developers have the resources required (O'Cathain et al., 2019). Therefore, each action needs to be addressed according to the relevance of the specific interventionand context.

1.12.3 Patient and Public Involvement

Participatory methods such as Patient and Public Involvement (PPI), reduce the disparity between researcher and participant and respect the participants' views by accounting forthem as full members of the team and co-researchers (Given, 2008). The modeling phase is of high importance, as it involves unravelling and identifying the active ingredients of the intervention (Craig et al., 2008). Consequently, patients and the public may be approached and actively participate during the modelling phase, incorporating a research process called PPI (Appendix I).

PPI is research planned and completed with or by patients rather than to, for, or about them and is a term usually associated with healthcare. The concept exists as Participatory Action Research (PAR) in behavioural and social sciences (Given, 2008, MacDonald, 2012). As patients and the public have their knowledge and expertise to advise researchers abouttheir condition, this leads to improvement of the quality, relevance, and impact on healthresearch. In addition, PPI may reduce the disparity of power between the researcher andthe patient. Three levels of PPI have been identified:

- Consultation- seeking views of patients and the public on key elements
- Collaboration- an ongoing partnership between researchers and patients
- Patient-led- patients conduct their own research and invite researchers

Figure 1—3 outlines the PPI process and the key steps to consider. Many steps may not be relevant to research and study, therefore this can be adapted accordingly.

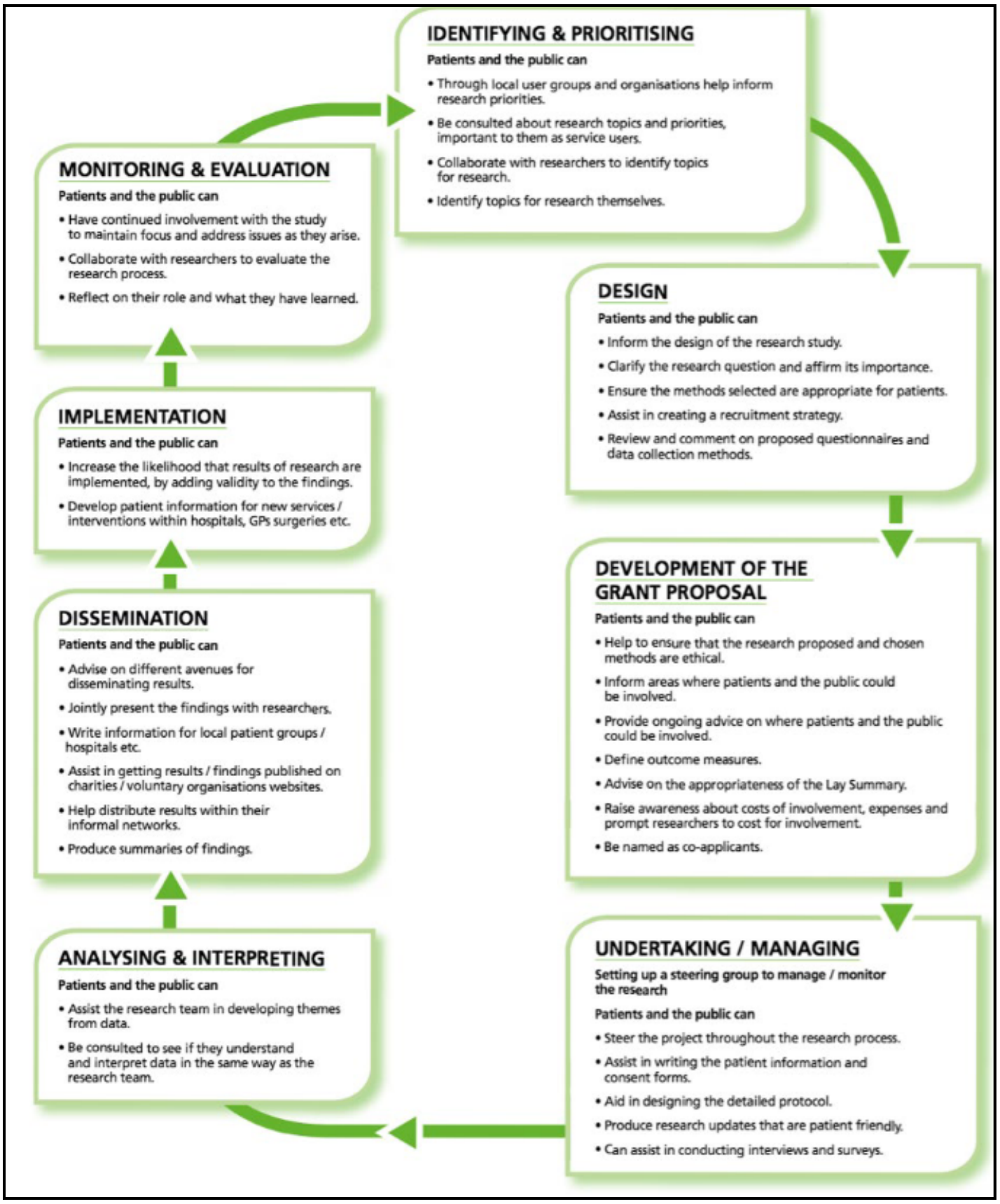


Figure 1—3 Steps to consider for PPI. Source: (Greenhalgh et al., 2019)

1.12.4 Potential study designs

RCTs represent the gold standard in the evaluation of healthcare interventions if they are appropriately designed, conducted, reported, and when randomisation is feasible. More importantly, RCTs are recognised as the best study design to assess the effect of an intervention and compare the efficacy or effectiveness of treatments (Relton et al., 2010).The use of control groups within RCTs is important and reflects how the intervention interacts with other contextual factors to produce an outcome. In any RCT or non-RCT bias may arise from confounding, selection bias, information bias and reporting bias. Relton et al. (2010) argued that exploratory and pragmatic RCTs may encounter difficulties in terms of recruitment, ethics, patients' preferences, and treatment comparisons. Therefore, the majority of RCTs fail to recruit sufficient numbers of patients and mainly focus on the causality to establish the effectiveness of an intervention rather than exploring how an intervention has worked, or understand the underlying mechanisms (Bonell et al., 2012). In addition, participants report concerns about information and consent for their participation as they are rarely being told the full information about the intervention before randomisation. Similarly, the usual double -blind placebo-controlled RCT cannot be utilised when investigating the efficacy of complex interventions for knee pain. This is because it is not possible to blind the study participants to whether they are in the active or control arm of the study. This has led to the use of pragmatic RCTs, in which the recruited participants are randomised to receiving an intervention, or continuing under the care of their GP (usual care). However, usual care may be offered outside the trial. The only incentive for the participant to take part in the trial is to receive the new intervention.

For example, when participants enter the trial, they are expecting to receive the intervention; but some may receive treatment as usual when allocated in the control group. This might lead to attrition and disappointment bias and participants might drop out of the study or report different outcomes in the outcome assessment. This is also known as participant ascertainment bias. Non-compliance or behaviour-modification bias may also occur when such an individual (after receiving education about the intervention) seeks better health care from

the health service, or modifies their lifestyle. Therefore, there may be a treatment effect which results from patient preferences rather from therapeutic efficacy. Similarly, during data collection in outcome assessment, staff members may unconsciously report better outcomes to those who received the intervention. To cope with patient preferences, a cohort design has been suggested where patients with treatment preferences are allowed their desired treatment and those who do not have strong views are randomised conventionally (Torgerson and Sibbald, 1998). An alternative to the latter, is when the strength and direction of patient preferences is elicited before randomisation, with all consenting patients randomised. This approach combines the advantage that is collecting data on the effect of preference on outcome, by maintaining the rigour of a full randomised design. The advantages of taking into consideration patient preferences in trials would produce additional information on the acceptability of the two treatments in different preference groups which would not have been available in the usual trial. To prevent all the aforementioned bias, multiple cohort RCT has been proposed. In this study design, a cohort of people with the condition of interest are recruited, and consented to be approached for either further questionnaire surveys, access to the GP surgery medical records and prescription data, data to be used as comparator for future RCTs, and approach for participation in future RCTs (Relton et al., 2010).

1.12.4.1 The feasibility stage

The aims and objectives of pilot and feasibility trials differ from those of other definitive studies and a lack of agreement in the research community exists about their definitions (Eldridge et al., 2016). A common characteristic though of pilot and feasibility studies is that both have intentions to plan a larger RCT and assess the effect of an intervention (Tickle-Degnen, 2013). The Consolidated Standards of Reporting Trials (CONSORT)statement (Schulz et al., 2010) a guideline designed to improve the quality and transparency reporting of RCTs, conducted a Delphi survey to distinguish between those terms. The authors addressed the concept of feasibility and studies that included this terminology referred to studies aiming to assess if a future RCT is doable. Their differenceshave also been highlighted by the National Institute for Health Research (NIHR, 2021) andare summarized in *Table 1—10*.

Table 1—10 Differences among pilot and feasibility studies

Pilot studies	**Feasibility studies**
A full trial of the main study that runs as a miniature to test if the components of the study can all work together	Pieces of research are done before the main study to answer the question can this study be done?
Assessment of the primary outcome	Do not evaluate the outcome of interest
Data can be incorporated to the data in the full trial for internal pilots	Estimate important parameters (e.g. eligibility recruitment, response rate, acceptability to the users)

The feasibility stage involves testing procedures for the acceptability of the intervention, estimating recruitment rates, and calculating sample sizes. A mix of qualitative and quantitative procedures is appropriate in this stage to investigate the barriers to participation in the trial and to estimate response rates (Craig et al., 2008). This stage isthe key, which will determine the progress and direction of the study where appropriate. It will either indicate a throwback in the development phase or progress into the evaluation phase depending on the preliminary results of the study. Acceptability and feasibility are two different concepts that should not be confused. Although, it is possible to assess the acceptability of an intervention to determine the feasibility of a larger RCT (Eldridge et al., 2016).

1.12.5 Evaluation of a complex intervention

MRC guidelines (Craig et al., 2008) highlighted the importance of conducting process evaluations nested in RCTs. The purpose of conducting process evaluation is to assess the quality and quantity of the implementation of the intervention (Moore et al., 2015a) and trials that collect rich qualitative data may identify potential barriers and facilitators to intervention implementation. Evidence suggests that it is more likely for simple and specific interventions to be delivered with high fidelity compared to those interventions with more complex elements (Dusenbury et al., 2003). This is because complex interventions have greater scope for variations in their delivery and therefore are more likely for their components not being implemented as they should. For example, strict fidelity measurement may not be appropriate as an intervention may work better if adaptation to local setting is allowed. Therefore fidelity with adaptation is suggested where the intervention implementers may bring changes to the original design or plan. Qualitative research can explore complex phenomena and delineate the actual ingredients of the intervention in the development phase, before theactual main RCT (Tong et al., 2007). However, such trials may not be able to draw definitive conclusions only based on qualitative data (Bonell et al., 2012). Therefore, process evaluation is useful to advocate, integrate and validate the pre-collected qualitative

or quantitative data by assessing fidelity of delivery, exploring factors affecting fidelity, and resolving possible challenges delivering the intervention.

1.12.5.1 *Understanding processes*

Process evaluation nested in trials aims to distinguish between naturally faulty interventions and those badly delivered (implementation failure) (Oakley et al., 2006). This sub-stage enhances the interpretation of the outcome results, by providing insights into why an intervention has failed, why a successful intervention has worked or has unexpected outcomes. An example of a process evaluation is fidelity assessment; the extent to which an intervention is delivered as intended (Swindle et al., 2018). Process evaluation, therefore, aims to assess the quality of implementation, clarify the causal mechanisms and identify contextual factors related to variation in the outcomes (Craig etal., 2008). Researchers should therefore not underestimate process evaluation that may consider conducting and reporting it with the same methodological rigor as the outcome evaluation. Fidelity assessment is crucial and needs to be addressed, as it determines if aprogramme has failed because of poor implementation or sub-optimal delivery (Swindle et al., 2018). Researchers have suggested using multiple methods such as self-reported checklists, video-recorded checklists for assessing fidelity (Huijg et al., 2015, McKenna etal., 2014) and to our best knowledge, few studies investigated the relationship between different those methods (Toomey et al., 2017).

1.13 **COVID impact statement**

The research team and I, were running the RCT to test the feasibility of a nurse delivering a complex intervention comprising of pharmacological and non-pharmacological components for knee pain due to OA. The recruitment was ongoing and two nurses were delivering the intervention. I was the blinded outcome assessor in the RCT. I received training from the research team at Nottingham City Hospital and Queens Medical Centre (QMC) on how to use all the equipment testing including questionnaires (WOMAC, SF-36, HADS, EQ-5D-5L), functional tests (sit to stand test, six-minute walk test) quantitative sensory testing (QST) and Muscle Function Test (MFT). I would collect all data on the aforementioned outcome measures at baseline, week 13, and week 26. The trial started on the 1st of November 2019 and was disrupted on 17 of March 2020 due to the covid-19 crisis. At baseline, data on 12 participants were collected on all the questionnaires and data on 10 participants on QST and MFT. Two participants completed week 13 before the trial stopped. It has become clear that a clinical trial that involves a lot of face-to-face contacts will not be feasible. My supervisors and I have changed the project and included a systematic review and a meta-analysis. However, I needed more time to complete this and a six-month extension was requested. My Ph.D. project has unfortunately been impacted by the COVID crisis with the recruitment paused in the clinical trial as outlined above. Prof. Abhishek Abhishek, Dr. Michelle Hall, Prof. Roshan das Nair and I, felt that starting a systematic review would have methodological challenges at this stage of my Ph.D. However, after much discussion, we agreed that I could be taught new skills remotely without any face-to-face contact. An observational study using the data available via IMWH and TEAM KP baseline questionnaires was also discussed. Following a couple of meetings, I have indicated that I would prefer to do a Systematic Review (SR) than do data analysis in the observational study. I am very pleased to say that I have received a lot of support from the aforementioned supervisors.

1.14 **Study Aim and Objectives**

This Ph.D. thesis aims to test the evidence base around the non-pharmacologic package of care for knee pain by conducting a systematic review and to conduct initial package development of a complex package of care for knee pain to be delivered by research nurses. The Ph.D. thesis is part of a larger body of work evaluating the feasibility of a cohort RCT of a nurse-led complex package of care for knee pain comprising the core pharmacological and non-pharmacological components. The Ph.D.'s objectives are:

[1] To systematically review the literature on complex interventions for knee pain due to OA and assess the quality of reporting of complex interventions, describe the different complex packages, and summarize the findings of all the included studies.

[2] To assess the fidelity of the nurse delivering the individual non-pharmacological components of the complex package of care for knee pain during the package development phase.

[3] To explore patient acceptability of the non-pharmacological intervention in the package development phase, and explore issues faced in delivery and resolve possible challenges to the delivery of individual components within a complex package

2. Chapter– A systematic review and meta-analysis of complex non-pharmacological packages of care for knee osteoarthritis and knee pain

2.1 Introduction

OA is the commonest form of arthritis and impacts the functional and social life of the individual (Sakalauskienė and Jauniškienė, 2010). The knee is commonly affected by OA and pain is the predominant symptom (Malfait and Schnitzer, 2013). Current non-pharmacological modalities refer to patient education, strengthening, and aerobic exercise, and weight loss advice if required. Pharmacological management aims to optimise analgesia, which follows the analgesic ladder and suggests paracetamol and topical NSAIDs ahead of oral NSAIDs and opioids.

Complex interventions are interventions with several active elements that work together to provide treatment effect (Moore et al., 2015a). Many studies have developed protocols for the care and management of OA and incorporated education on OA, aerobic and strengthening exercise, weight loss advice, and pharmacy review (analgesics use), in their targeted interventions (Atukorala et al., 2016, Dziedzic et al., 2014, Eyles et al., 2014, Hay et al., 2006, Knoop et al., 2013, Skou and Roos, 2017, Thorstensson et al., 2015). A systematic review describing them has not been conducted to date. The two conditions for experimental interventions to be adopted as standard care are to be effective and be implemented with a minimum implementation fidelity standard. Implementation fidelity in complex interventions for knee OA is poorly recognised and reported. A few studies (Dziedzic et al., 2014, Thorstensson et al., 2015) report fidelity of delivery and acceptability of the intervention. There is no agreed definition of fidelity and some papers refer to that term as "implementation fidelity", "treatment fidelity" and even treatment "integrity". A previous systematic review (Ang et al., 2017) identified and summarised the key strategies to improve and assess the level of reporting of implementation fidelity in RCTs of palliative care complex interventions.

Variation in the quality of administration of interventions may affect the results of RCTs and reviews of complex interventions need to consider that (Herbert and B∅, 2005). Hoffmann et al. (2013) highlighted inadequate description of interventions with more than 60% of trials of non-pharmacological interventions missing essential information about the intervention. There is also poor quality of reporting of these interventions. Further research is, therefore, needed, to evaluate the reporting of those complex interventions and assess their overall efficacy. The main focus of this systematic review is therefore, to identify if a complex intervention for knee pain due to OA is effective and assess the strategies used to report implementation fidelity in the identified studies.

2.2 Methodology

2.2.1 Data sources and search strategy

A literature search was performed on the electronic databases Ovid MEDLINE, EMBASE, AMED, PsycINFO, and CINAHL from inception to 29/9/2020 and Google Scholar (first 100articles) in English. A search strategy was built up and comprised vocabulary terms, text words, synonyms, and related terms for each concept. Exploded Medical Subject Heading(MeSH) terms and text words were combined using the Boolean operators "AND" and "OR". Boolean operators are words that connect the search terms or keywords to broadenor narrow the results retrieved. The three Boolean operators comprise "AND", "OR", "NOT"and sets of terms were developed for the healthcare condition, the intervention, and the study design. We avoided using the "NOT" operator to avoid the danger of inadvertently removing search set records that are relevant as reported in the Cochrane guidelines (Higgins, 2021). Examples of the included search terms comprised: a) [knee osteoarthritis] OR [knee pain], b) [physical activity] OR [exercise] OR [physiotherapy] OR [integrated rehabilitation] OR [resistance training] AND [dietary restriction] OR [meal replacement] OR [weight loss] OR [caloric restriction] OR [obesity], c) [RCTs] OR [clinical trials], d) [Self- management] OR [patient education]. A full description of the search strategy is documented in Appendix II. Following the development of the search strategy, we evaluated the initial search strategy with all three components of the intervention (exercise, weight loss and self-management) combined together. However, when the search strategy was

repeated with the self-management being a separated element then we were able to obtain more citations. A methodology for creating exhaustive search strategies has been published by Bramer et al. (2018) was followed and consisted of the following steps: 1) determine a clear and focused question, 2) describe the articles that can answer the question, 3) decide which key concepts address the different elements of the question, 4) decide which elements should be used for the best results, 5) choose an appropriate database and interface to start with, 6) document the search process in a text document, 7) Identify appropriate index terms in the thesaurus o the first database, 8) identify synonyms in the thesaurus, 9) add variations in search terms 10) Use database-appropriate syntax, 11) optimise the search, 12) Evaluate the initial results, 13) Check for errors, 14) Translate to other databases and 15) test and reiterate. The secondary search included the reference lists of pertinent articles, relevant systematic reviews, and RCT protocols. Citations and abstracts retrieved from this search were downloaded to Endnote X8 (licensed to the University of Nottingham) and duplicates removed. Citations from Endnote X8 were then imported to Covidence for screening. The latter is a systematic reviews production software, which enables multiple reviewers to work efficiently, and facilitates title/abstract screening, full-text screening, data abstraction, and quality assessment (Babineau, 2014).

2.2.2 Eligibility of studies

Types of studies to be included: RCTs including either pilot, feasibility, cluster, or quasi-experimental that examined the effects of patient education, exercise, and weight loss advice in adults with knee OA in all settings. This particular design (RCT) has been selectedas it provides the clearest evidence for the benefits of healthcare interventions (Higgins, 2021). A quasi experimental study-design sometimes called pre and post intervention does not use randomisation. The lack of randomisation in this design is a weakness that may cause the inability to control for confounding. Regression to the mean is another potential treat of quasi experimental study-design, and authors may conclude that the effect of the intervention is due to the intervention, while in reality is due to chance factor (Harris et al., 2006).

Intervention(s): Complex interventions comprising at least three components: patient education, exercise, and weight loss advice with or without any other non-pharmacological intervention (e.g. cognitive behavioural therapy, orthotics) were included. Studies were eligible for inclusion if any healthcare professional delivered education for OA. Handing of only a leaflet about OA was not considered as delivery of patient education. Where education on OA was not explicitly stated in the text, the authors of the original paper were contacted to provide further information. The comparator was any intervention of no treatment, waiting list, usual care, placebo, any single non-pharmacological intervention, or pharmacological treatment. Individualisation of intervention was assessed if the healthcare professionals negotiated personal goals with the participants.

Population: Eligible RCTs included people classified as having knee OA using any of the following criteria; grade ≥ 2 according to the KL classification system (Kohn et al., 2016),meeting the ACR criteria for knee OA (Altman et al., 1986), self-reporting knee pain on most days of the previous month (O'reilly et al., 1996), or physicians' diagnosis OA. Studies with rheumatoid arthritis or any other type of inflammatory arthritis such as psoriatic arthritis, systemic lupus erythematosus, polymyalgia rheumatic, or InflammatoryBowel Disease (IBD) associated arthritis were excluded. A hierarchy of exclusion to determine the basis on which articles were excluded and the reason for that exclusion was developed by the study team (*Table 2—1*).

Table 2—1 Level of hierarchy with reasons for excluding titles, abstracts and full texts.

Language	Excluded if they are not in full version English.
Study design	Excluded if they are case-control studies, cross-sectional studies, case reports, cohort studies, and case series.
Type of publication	Excluded if are abstracts, books, protocols, or reviews.
Targeted population	Excluded if they include rheumatoid arthritis, psoriatic arthritis, or any other type of inflammatory arthritis apart from knee OA.
Age of the population	Excluded if their population is <16 years.
Component of the intervention	If they only include surgical or pharmacological interventions.
Eligibility criteria of the population	Excluded if their eligibility criteria of the population is not reported or is reported and consist of any other apart from the following: • Grade 2 or more according to the KL classification system • Meeting the ACR criteria for knee OA • Self-reporting knee pain on most days of the previous month • Physician diagnosis of knee OA
Number of components of the intervention	Studies are excluded if the main intervention is made up of two or fewer non-pharmacological components, e.g. exercise and education only will not be included or studies of surgical interventions.

Articles were being excluded based on the first level identified in the hierarchy only and that level will be recorded.

Outcome(s): The primary outcome was knee pain. The Western Ontario McMaster Universities Arthritis Index (WOMAC) and the Knee Injury and Osteoarthritis Outcome Score (KOOS) pain subscales were used to measure knee pain due to OA as they are both knees specific and KOOS was developed as an extension of WOMAC but for younger populations (Roos and Lohmander, 2003).

Secondary outcomes included patient-centred outcomes such as physical function measured with WOMAC or KOOS physical function subscales, quality of life, psychological

outcomes such as anxiety or depressions, consumption of analgesics, and NSAIDs or opioids.

Study time point(s): Outcomes reported at different time points and during the follow-up periods were collected. A single time-point for each study was used to analyse data and this was the clinically important time point for that particular study. That refers to the time-point the trial had the statistical power to detect statistically significant treatment effects. The commonest time point across all trials was selected therefore as the primary outcome point for analysis. This was used to maximize the data available, however, this might be vulnerable to biases.

2.2.3 Data collection

Study identification: Three reviewers (AA, MH, and PAN) took part in the screening process. PAN initially screened 10% of the identified titles and abstracts using Covidence software. AA and MH independently screened 5% each and overall agreement after verbaldiscussion was assessed. This process was repeated for full-text screening. The reasons for exclusion were recorded and are reported in Figure 2—1. A third reviewer (RdN) was only involved where discrepancies arose.

2.2.4 Data extraction and management

Data were extracted by a single reviewer (PAN) using a specifically developed data extraction form (Appendix III) and then transferred data to a structured database that was developed in Microsoft Access for data entry. Two independent reviewers (AA and MH) validated the process by independently extracting data from 10% of the studies. Disagreements between reviewers were resolved through discussion, with the involvement of a third reviewer if required. However, a third independent reviewer was not required on this occasion. Data included the following information:

- General study information: title, authors, country, the language of publication, year of publication, funding source, study setting (primary or secondary care), eligibility criteria, number, and nature of study arms
- Study methods: design (parallel or cross-over), randomisation procedure, allocation, blinding (participants, people administering treatment, outcome assessors), duration of the study, analysis method (e.g. intention-to-treat), and fidelity of delivery of the intervention
- Participant characteristics: age, gender, ethnicity, education, level of economic deprivation, no. of participants randomised to groups, baselinecharacteristics, no. of participants dropped out, and loss to follow-up.
- Intervention(s): description of interventions, description of the control group,and completeness of intervention reporting
- Outcomes: primary and secondary outcome measures, adverse events, follow-up time points, and patient acceptability.
- Results: for each outcome and time-point of assessment, including a measure ofvariation.

2.2.5 Study quality appraisal

Risk of Bias: Assessing methodological quality is an important step while conducting systematic reviews. The methodological quality of the studies was assessed by using the Revised Cochrane risk-of-bias (RoB 2) tool for randomised trials (Sterne et al., 2019). RoB2 is characterised by five bias domains arising from the randomisation process, deviation from intended intervention, missing outcome data, selection of the reported result, and overall bias. PAN assessed the methodological quality of all papers and two independent reviewers (AA, MH) validated the process by independently assessing 10% of the included studies. Pre-specification of outcomes in RCTs protects against outcome switching (Kahan and Jairath, 2018). For example disregarding non-significant outcomes in favour of outcomes with better results. This was determined if the authors had a published protocol that listed and well defined the outcomes of the study or registered their protocol at ClinicalTrials.gov.

Fidelity of delivery: Reporting of implementation fidelity was assessed using a previously published 40-item checklist with guidelines on how to score each item (Ang et al., 2018). Strategies are identified and rated according to the two key core elements for assessing fidelity: delivery of treatment, and treatment receipt (section D, Appendix III). Each item is rated on the checklist as present sufficiently ("++") if there was a detailed reporting for that item, ("+") for present insufficiently (if it is briefly mentioned), and "Absent but should be present". Comment textbox was added in the results section to justify the rating of each item. Key strategies for treatment delivery, comprised the usage of treatment manual, usage of implementation checklist, site visits to ensure adherence to the intervention plan, interviewing patients on their experience, examining medication prescription, preventing exposure between the intervention and the control group and using a cluster RCT. Key strategies for treatment receipt included: a health literacy component assessment, patient able to recall the intervention assisting with understanding of medical terminology, providing access to information, answering questions, verifying understanding, and providing an information pack.

Quality of reporting of interventions: Reporting of study interventions was assessed with the TIDieR checklist (Hoffmann et al., 2014). The overall purpose of the TIDieR checklist is to guide authors to describe interventions in sufficient detail to allow for replication. The checklist includes the minimum items required for describing an intervention. TIDieR assesses intervention reporting by asking questions on why, what (materials), what (procedure), who provided, how, where, when and how much, tailoring,modifications, how well (planned), how well (actual). The original authors were contacted to request any data not reported. Items were assessed using a 3-point Likert scale not reported (✗), unclear (?), and adequately reported (✓). We combined the items of the TIDieR checklist for the intervention and the control group to create a summary score. For example, if an item has been adequately reported for the intervention and control group,a score of two was ascribed. If the item was unclear, a score of one was given, and if it was inadequately reported zero points.

Therefore, a TIDieR summary score was created by summing the number of checklist items and was able to provide a combined measure of the completeness of reporting for both intervention and control treatment strategies as evident in previous studies (Yamatoet al., 2018). A single measure of reporting completeness that considers the reporting ofmultiple treatment arms with the same level of detail expected for each treatment arm ofthe trial. The use of a summary score may facilitate the evaluation. Table 2—2 presents the scoring process based on information presented or not for the intervention and control group. A previous study (Yamato et al., 2018) evaluated the properties of TIDieR summary score. They used Rasch analysis and suggested that the data fit the scale and can be used to provide a combined summary score of completeness of reporting for both the intervention and the control treatment groups.

Table 2—2 Instructions for reporting scores on two treatment groups (Yamato et al., 2018)

	Intervention group	**Control group**	**Score**
Rating for each item	No	No	0
	No	N/A	0
	Yes	No	1
	No	Yes	1
	Yes	Yes	2
	Yes	N/A	2

2.2.6 Strategies for data analysis and synthesis

Descriptive synthesis was conducted to present participant characteristics (sample size, mean age, mean BMI kg/m^2, female percentage) at the study level, quality of the intervention completeness, and reporting of fidelity. A narrative synthesis was the approach to follow to bring the results of the included studies together and drawconclusions. According to the Centre for Reviews and Dissemination at the University of York, a narrative synthesis of the

results should be the first methodological step to use to decide what other methods are appropriate to follow (Bangert-Drowns et al., 1997). Therefore, preliminary synthesis of findings of the included studies was conducted for each study and its characteristics (sample size, population, design, intervention delivery, intervention, comparator, outcomes, outcome measures, time points, and results). This was performed using an iterative process by organising and summarising the features andthe results of the identified studies into tables providing a general framework. Following this, relationships within the data were explored. Narrative synthesis was selected as the primary approach for synthesis as we would expect a considerable amount of heterogeneity between the identified studies. We combined at least three interventions and had different comparators. Narrative approach has been considered useful to investigate heterogeneity across RCTs and explore the active ingredients of the intervention (Richard et al., 2009).

Meta-analysis: A meta-analysis was used to present and pool the results of the identified studies statistically. Meta-analyses are conducted to assess the strength of evidence, determine if an effect exists (either positive or negative), and provide a summary estimate of effect.

To allow a comparison between continuous outcomes reported by the studies, effect sizes (ES), standardised mean differences (SMD), and 95% confidence intervals (CI) were calculated for primary and secondary outcomes. SMD was preferred over mean difference (MD) as a summary statistic because the included studies used different scales to measure the same domain (e.g. pain). Where the heterogeneity of the data allows comparison, meta-analysis was conducted using a random-effects model to determine the effectiveness of the intervention for studies with similar control groups (pharmacological, no treatment, placebo, waiting list, usual care, or other non- pharmacological/non-surgical interventions). A random-effects model was selected over the fixed-effects model. The latter does not take into account the variability (heterogeneity) among the studies and an assumption is made the true effect size of intervention is the same in every study, and that the observed differences between study results are only due to chance and not because of variability (JPT Higgins, 2011). The examination of heterogeneity is vital to generate

new hypotheses.

Sub-group analyses were conducted for interventions that were delivered online, face-to-face, on individual and group levels. This is as a recent study found that internet-based first-line delivered treatments for knee OA may reduce pain and improve physical functionwhen compared to usual care (Gohir et al., 2021). Moreover, whether the non- pharmacological treatments for knee OA are either delivered in one-on-one sessions or a group-based approach, may be a reasonable model of delivery but which model is more effective is not yet known according to Allen et al. (2016a). Moreover, there is some evidence that interventions with underpinning psychological theories are more effective interms of behaviour change but this may not necessarily be detected when using pain outcomes (Keefe et al., 2008). Therefore, sub-group analyses were also conducted for studies that utilised learning theories as part of their interventions. Studies that used multidisciplinary approaches, and those that used intra disciplinary approaches were also explored in subgroup analysis. A multidisciplinary team consists of a diverse range of clinicians delivering services seamlessly to individual patients using a wide range of skills, but may not interact with each other. Interdisciplinary/interprofessional team comprise a diverse range of clinicians delivering services using a wide range of skills, but roles sometimes overlap, which can conflict with individual professional identity. Intra disciplinary approach is when a professional from one discipline only (i.e. physiotherapist only, nurse only) was involved in the delivery of the intervention (Jelley et al., 2010). The robustness of themeta-analysis results was examined by undertaking sensitivity analyses.

Assessment of heterogeneity: Identified studies that are brought together in a systematic review usually differ, and thus, different types of heterogeneity exist (JPT Higgins, 2011). Clinical heterogeneity, described as the variability among the participants,interventions, and outcomes; methodological heterogeneity refers to the variability amongthe risk of bias/design; and statistical heterogeneity. The latter term is a consequence ofeither clinical or methodological diversity and refers to variability among the interventioneffects being evaluated. Considering all these, it is important to identify and measure theconsistency among the results of the different studies.

Heterogeneity, therefore, was assessed initially by visually inspecting the summary table of the included studies and theforest plots for between-study heterogeneity. In addition, the Higgins I^2 statistic was calculated (Higgins et al., 2003). Visual inspection may be more informative than I^2 values for a small number of trials. I^2 measures the degree of inconsistency among studies and ranges from 0-100% where 25%, 50%, and 75% are considered low, moderate, and highvalues.

Assessment of publication bias: Studies with non-significant findings are more likely to remain unpublished and therefore, less likely to be included in a systematic review or meta-analysis (Peters et al., 2006). Moreover, it has been shown that lower-quality trialsare difficult to find raising the concern that bias could be introduced through extensive literature searches (Egger et al., 2003).

A funnel plot is a scatter plot with the intervention effect estimates plotted against the standard error of the study and is used to detect publication bias by examining its asymmetry (Sterne et al., 2011). The funnel plot was used as a method to assess for publication bias in this study. This meta-analysis followed the recommendations on testingfor funnel plot asymmetry published by the BMJ (Sterne et al., 2011).

Sensitivity analysis: Sensitivity analysis was conducted to explore relationships between duration of trial and effect sizes. The intervention duration was subtracted from the primary outcome assessment time point and the effect sizes data were collected and analysed at time intervals week zero and weeks 2-20. We investigated whether the interval between the end of the intervention and primary outcome assessment influences the overall effect size.

Study reporting: The review is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). The protocol for this systematic review is registered with Prospero (Polykarpos Angelos Nomikos, 2020).

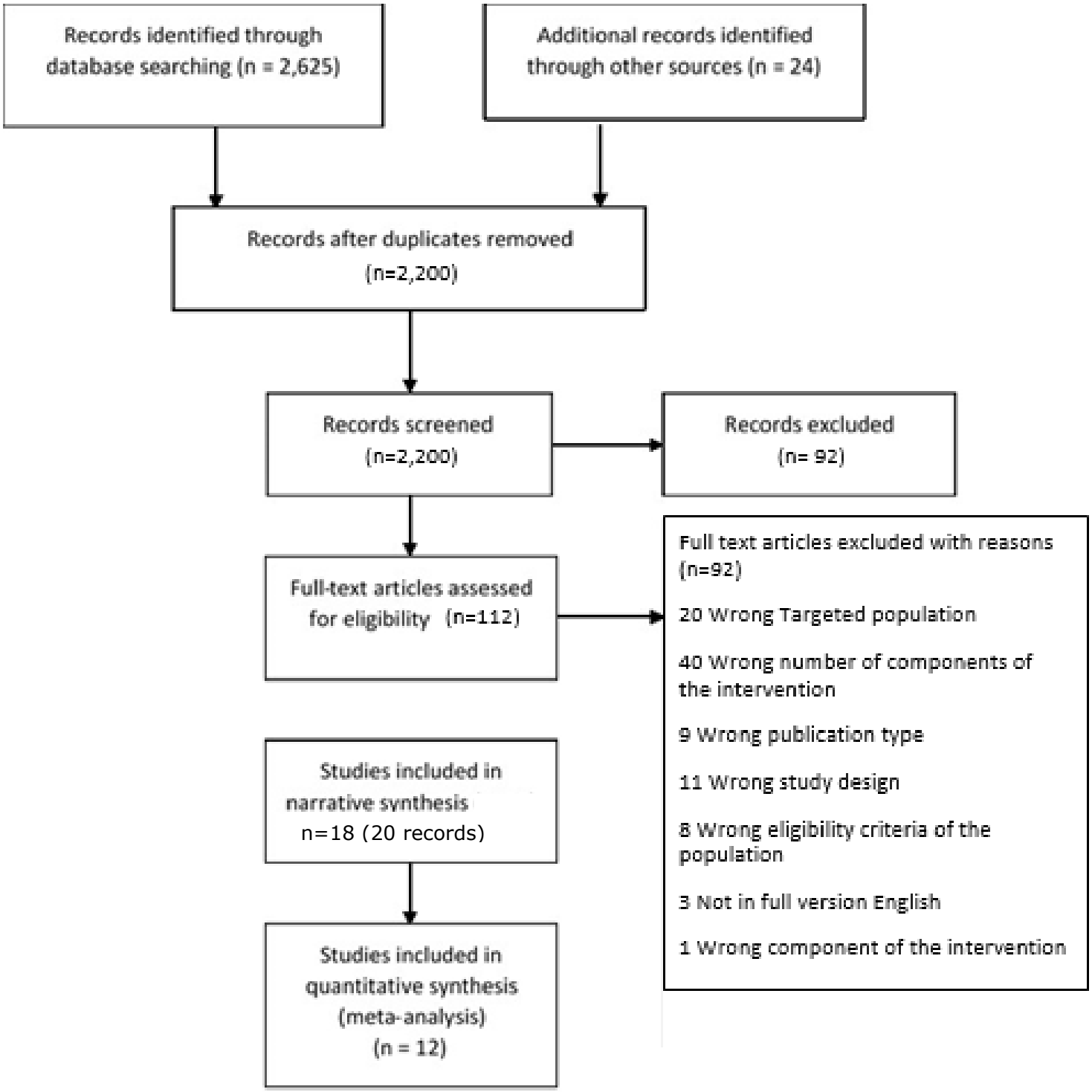
2.3 Results

This section presents and discusses the results of the systematic review and meta-analysis undertaken. The study summarizes the evidence of all previous studies that delivered or evaluated complex (non-pharmacological and pharmacological) packages of care for knee pain due to OA in RCTs and delivered by any allied health care professional.

2.3.1 Selection of studies

Electronic databases and hand searches yielded 2,649 titles and abstracts, of which 449 duplicates were removed (Figure 2—1). After duplicate removal, 2,200 citations were retrieved for the title and abstract screening. Agreement with the independent reviewers (AA and MH) on study selection was 96%. Overall, 112 citations progressed to full-text screening, of which 92 were excluded with the reasons for exclusion reported in Figure 2—1. Twenty studies were found eligible to be included in narrative synthesis and twelve in the meta-analysis. All studies were written in English.

Figure 2—1 PRISMA flow diagram



2.3.2 Study Characteristics

Identified studies were published from 2007 to 2020 and conducted in America (Brazil, Canada, USA), Europe (France, UK), Asia (Thailand, Singapore, Hong Kong, Iran), and Australia. Rezende et al. (2017) presented results in three different articles (de Rezende et al., 2013, de Rezende et al., 2016), but we merged their results and considered the paper as one study. Therefore, a total number of eighteen studies were included in a narrative synthesis. Seven studies (39%) were delivered in the community, four (22%) in primary care, six (33%) in secondary care and one (6%) was home-based. Eleven studies (61%) were single centre and seven (39%) were multicentre. Thirteen studies (72%) were parallel-group RCTs, three (17%) were cluster RCTs, one (6%) was quasi-experimental, and one (6%) was feasibility. Four studies did not report the funding source and one declared no funding. All studies reported the eligibility criteria of the population. In particular, eight studies (44%) used the ACR criteria for knee OA, four (22%) used grade ≥2 KL classification criteria, four (22%) physician diagnosis OA, and two (11%) knee pain on most days of the previous month. Regarding the number of arms, fourteen RCTs (78%)had two arms, three RCTs (17%) had three arms, and one (5%) had four. All studies obtained ethical approval.

2.3.3 Study and intervention characteristics

Review of participant numbers at each stage of recruitment: In total, 9,374 people with knee pain due to OA were approached to take part, of which 5,438 met the inclusion criteria. The number excluded was 6,760 with 1,877 declining to participate. Overall, 3,069 patients (72.6% were women) with knee OA and mean age of 62.1 years (SD 8.7) and body mass index of 30.9 (SD 6) kg/m^2 were randomised into groups. Of those, 639 have dropped out. Information about the number of patients approached/screened before randomisation was not provided by Coleman et al. (2012). Further details of the participants' characteristics for each study are displayed in Table 2—3. The final frameworkof narrative synthesis developed providing the features and the results of the identified studies are presented in Table 2—4.

Table 2—3 Participant characteristics for each study

Author (year)	Sample size (n)	Age mean (SD)	BMI mean (SD) kg/m^2	females %	Inclusion criteria
Marra et al. (2012)	139	61.8 (8.3)	31.1 (12.3)	57	Knee pain on most days of the previous moth
Coleman et al. (2012)	146	65 (8.2)	35.4 (7.3)	74.5	Physician diagnosis OA
Bennell et al. (2017)	148	61.2 (7.1)	31 (12.2)	56	Knee pain on most days of the previous moth
Robbins et al. (2020)	171	63.1 (7.4)	35.4 (7.3)	64	KL grading method
Palmer et al. (2014)	224	61.4 (10.5)	29.5 (9.2)	62.7	ACR criteria for knee osteoarthritis
Hurley and Walsh (2012)	418	67 (7.2)	30.2 (5.7)	70	Physician or doctor-diagnosed knee OA
Mecklenburg et al. (2018)	162	46.4 (12)	27.4 (4.7)	34.5	ACR criteria for knee osteoarthritis
Saraboon et al. (2015)	80	67.4 (6.8)	26.4 (2.3)	92.5	ACR criteria for knee osteoarthritis
Ravaud et al. (2009)	327	64.3 (8.2)	30.7 (3.7)	74.8	ACR criteria for knee osteoarthritis
Farr et al. (2010)	293	55.2 (6.9)	27.6 (4.2)	74.7	KL grading method
Yip et al. (2008)	95	64.1 (10.7)	Not available	85.5	ACR criteria for knee osteoarthritis

Messier et al. (2013)	454	66 (6)	33.6 (3.7)	71.7	KL grading method
Taglietti et al. (2018)	60	68 (6.3)	29.8 (1)	68.2	ACR criteria for knee osteoarthritis
Kawi et al. (2015)	16	60.9	34.1	100	Physician or doctor-diagnosed knee OA
Tan et al. (2020)	20	63.8 (8.3)	Not available	85	KL grading method
Rezende et al. (2017)	195	64.4 (9.1)	31.4 (5.5)	77	ACR criteria for knee osteoarthritis
Khachian et al. (2020)	80	58.5	Not available	72.5	Physician or doctor-diagnosed knee OA
da Silva et al. (2015)	41	58.6 (7.1)	29.3 (4.5)	86.8	ACR criteria for knee osteoarthritis

Table 2—4 Study and intervention characteristics

Author (Year)	Sample Size (intervention, control)	Participant characteristic	Design	Intervention delivery	Intervention	Comparator	Outcome (measures)	Time points (week)	Results
Marra et al. (2012)	139 intervention:73 control: 66	Knee pain Age ≥ 50 years	Cluster RCT	Pharmacist Physician Physiotherapist	Medication review Education Nutrition Individualised home-exercise programme	Control group: Pamphlet on knee OA by Arthritis Society plus usual care	Primary: Quality of care for OA (Arthritis Foundation quality indicators). Secondary: Knee pain and function (WOMAC), lower extremity function (LEFS), generic quality of life (PAT-5D), and the Health Utilities Index Mark 3 (HUI-3)	13 and 26	WOMAC pain, function, PAT-5D, LEFS, and HUI-3 improved in the intervention group compared to control group at 13 and 26 weeks
Coleman et al. (2012)	146 intervention:71 control:75	Knee OA Age ≥ 18 years	Parallel group RCT	Nurse Physiotherapist Occupational Therapist	Education on OA, Self-management skills Medications Correct use of analgesia Pain management Fitness and exercise Joint protection	Control group: Usual care (standard medical management for knee OA)	Primary: Pain, stiffness, and physical function (WOMAC), and quality of life (SF-36). Secondary: Pain (VAS), functional mobility (TUG), isometric strength of hamstrings and	8 and 26	WOMAC pain, physical function, total scores, hamstrings strength in both legs, and SF-36 significantly improved in the intervention group compared to control at 26 weeks

					Nutrition and weight control		quadriceps (Mecmesin force gauge dynamometer).		
Bennell et al. (2017)	148 intervention: 74 control: 74	Knee pain Age ≥50 years	Parallel group RCT	Physiotherapist	Internet delivered treatments: Educational material about OA, exercise, healthy eating, pain management, emotions and medications. Eight modules for pain copings skills. Seven skype sessions with the physio	Control group: access to the educational material only	Primary: Pain during walking (NRS), physical function (WOMAC). Secondary: Knee pain (WOMAC), Quality of life (AQoL-2), Self-efficacy (ASES), Pain catastrophizing (PCS), Coping attempts (CSQ)	13 and 39	WOMAC pain and function significantly improved in the intervention group compared to control group-changes sustained at 39 weeks. Significant improvements for the intervention group in all secondary outcomes at both time points.
Robbins et al. (2020)	171 intervention: 87 control:84	Medial Tibiofemoral OA Age ≥50 years	Parallel group RCT	Pharmacist Dietician Occupational Therapist Nurse	First step: home-based diet and exercise by OAHWL programme with education on OA. If disease remission not achieved allocation to CBT, knee brace, and muscle	Control group: educational pamphlet about OA plus usual care	Primary: Disease remission (yes/no) Secondary: Pain intensity (VAS), functional impairment (WOMAC function sub-scale), body weight loss (%), physical performance (TUG), fast-paced walk test (40m),	20 and 32	VAS pain and WOMAC function significantly improved in the intervention group compared to control at 20 weeks. Intervention group showed greater improvement in function compared to

					strengthening exercise		weight/height^2 (BMI), quadriceps strength (isometric knee extensor strength test), severity of depression (DASS-21), Knee ROM and knee alignment (goniometry)		control at 32 weeks but no difference in pain. Greater weight loss in the intervention group compared to the control at 20 and 32 weeks.
Palmer et al. (2014)	224 intervention A:73 intervention B:74 intervention C:77	Knee OA Age ≥ 18 years	Parallel group RCT	Physiotherapist	Arm A: active Tens and knee group (OA education, exercise, weight loss)	Arm B: Sham Tens and knee group Arm C: Knee group	Primary: Physical function (WOMAC). Secondary: Pain, stiffness and total scores (WOMAC subscales).	3, 6, 12 and 24	WOMAC function and total scores improved over time for all arms. No differences between trial arms. Improvements maintained at 24 weeks.

Hurley and Walsh (2012)	418 intervention: 278 control: 140	Knee pain Age ≥ 50 years	Cluster RCT	Physiotherapist	Exercise-based rehabilitation programme ESCAPE-knee pain (exercise, education, self-management, nutrition) and usual care (services physician considered appropriate).	Control group: Usual care	Primary: Physical function (WOMAC). Secondary: Pain (WOMAC), Functional performance (AFPT), exercise-related health beliefs and self-efficacy questionnaire (ExBeliefs), Anxiety and Depression (HADS), condition-specific health-related quality of life (MACTAR), quadriceps strength.	6, 26, 78 and 130	WOMAC function largely improved initially for the intervention group compared to control but these changes declined over time. Secondary outcomes showed similar pattern of results apart from improvement in exercise-health belief and self-efficacy, which sustained.
Mecklenburg et al. (2018)	162 intervention: 101 Control: 61	Knee pain Age > 18 years	Parallel group RCT	Profession of healthcare provider is unclear (personal health coach)	Hinge health digital care programme sensor guided exercise, OA education, CBT, psychological support, weight loss, activity tracking and usual care.	Control: Usual care and knee care education (importance of self-care, setbacks knee pain, communication)	Primary: Pain and physical function (KOOS). Secondary: Pain and stiffness (VAS).	12	KOOS pain subscale and function improved in the intervention group compared to control. VAS pain and stiffness showed improvement.

Saraboon et al. (2015)	80 intervention:40 control: 40	Knee pain Age ≥ 50 years	Parallel group RCT	Nutritionist	Education programme about OA. Weight reduction programme and exercise either individually or in groups and home visits.	Control: Knee OA booklet and video compact disk	Primary: Knowledge about OA (10 true/false questions). Secondary: Illness representation of OA knee (0-10 response scale), health outcomes in terms of health behaviours (health behaviour questionnaire), knee pain (NRS), ROM (goniometer), body weight, movement ability (TUG).	8	OA knowledge, illness representation, health behaviour, and ROM, improved in the intervention group compared to control. Mean scores for knee pain and body weight were lower in the intervention group than in the control.
Ravaud et al. (2009)	327 intervention: 146 control: 181	Knee OA Age 45-75 years	Cluster RCT	Rheumatologist	Education and advice on OA, exercise regimen, weight loss information and proposed strategy to lose weight.	Control: Usual care	Primary: Weight and time spent on physical exercises (Baecke index). Secondary: Pain on movement during the 48 hours (NRS), global assessment of disease activity (NS 0-10), physical function (WOMAC subscale), quality of life (SF-12).	2, 4, 17, and 52	At 17 weeks, reduction in pain and weight for the intervention group compared to control. Increase in time spent on physical exercises in intervention group. No difference in secondary outcomes apart from pain and

									global assessment. At 52 weeks, intervention group showed better scores on WOMAC function, pain level, SF-12 and global assessment
Farr et al. (2010)	293 intervention A:100 intervention B:98 intervention C:95	Knee OA Age 35-68 years	Parallel group RCT	Physical Trainer	Arm A: Resistance training and self-management	Arm B: education on OA, exercise principles, stress and pain management foot care, analgesic Medication nutrition Arm C: exercise regimen (stretching and balance, ROM and flexibility, muscle strength, and aerobics).	Primary: Levels of moderate or vigorous-intensity physical activity (accelerometer). Secondary: Leisure time physical activity and exercise habits (ACLS). Knee pain [WOMAC subscale (0-100)], exercise session attendance (%).	13 and 39	Both groups increased MVPA from baseline to 13 weeks but only the RT group maintained those changes at 39 weeks. The RT group maintained higher MVPA levels than SM group.

Yip et al. (2008)	95 intervention: 45 Control: 50	Knee OA	Parallel group RCT	Nurse	ASMP and exercise: self-management, education about OA, goal oriented exercise (stretching, walking and tai chi), using medications, healthy nutrition, sleep and routine conventional treatment.	Control: routine conventional treatment	Primary: Strength of a person's belief in his/her ability to control various aspects of arthritis (ASE scale). Secondary: Pain, pain at night, pain while switching from siting to standing and fatigue (VAS). Self-rated health (1-5 scale), self-reported daily activities limitation (HAQ) and number of unplanned arthritis-related medical consultations	1, 16 and 52	Significant improvement for the intervention group in ASE at 52 weeks. Intervention group showed decrease in pain, pain at night, and pain during walking but not for pain while switching from a sitting to a standing position at 52 weeks. Significant increase in self-rated health and decrease in medical consultations.

Messier et al. (2013)	454 intervention A:152 intervention B: 152 Control:150	Tibiofemoral OA or Tibiofemoral plus patellofemoral Age ≥ 55 years	Parallel group RCT	Not reported	Arm A: Diet: energy intake deficit, nutrition education and behavioural sessions. Exercise: aerobic walking, strength training, aerobic phase and cool down. Education on OA was provided- author was contacted to provide that information.	Arm B: Diet only Control: Exercise only	Primary: Knee comprehensive forces (biomechanical joint loading-N) and inflammation (plasma IL-6 in pg/ml) Secondary: Pain and function (WOMAC subscales). Health related quality of life (SF-36). Retention (%) and adherence to exercise (number of sessions completed), weight loss (kg) and body composition (fat mass), mobility (gait speed and 6MWT).	26 and 78	Lower comprehensive forces and inflammation levels in Arms A, B compared with control. At 78 weeks, intervention group had less pain compared with B and control in WOMAC pain and function. Intervention group walked 0.04m/s faster than control. Greater weight loss in arms, A, B compared with control.
Kawi et al. (2015)	16 intervention A:8 intervention B:8	Knee OA Age ≥ 50 years	Pilot quasi experi mental	Physiotherapist Nurses	Arm A: Progressive walking and online SM program (duration of the walking sessions was progressed,	Arm B: Progressive stepping + online SM program (height of the steps was progressed)	Primary: Knowledge, skills, behaviours, and confidence of individuals in self-managing their chronic illness (PAM), change in activation scores	6 and 26	Activation scores to SM were significantly higher after intervention in all participants and when evaluated according to exercise groups.

					participants committed to the online static and dynamic modules)		to SM and Activation levels		Magnitude of change in mean activation scores similar across both.
Tan et al. (2020)	20 intervention: 10 control:10	Knee pain Age ≥ 45 years	Feasibility RCT	Orthopaedic surgeons Physiotherapist Dietician Psychologist Social worker	Assessment and education exercise therapy Nutrition and dietetics Psychological support	Control: Referral to the outpatient physiotherapist. Lifestyle modifications and exercise therapy.	Primary: Symptoms, pain, function, (daily living), function (sports, recreational activity) and quality of life (KOOS). Secondary Pain, symptoms, function (KOOS), quality of life (EQ-5D-5L), functional assessment (TUG), BMI, psychological related outcomes (PEG, PHQ-4), diet and adverse events	12	Improvements in KOOS, KOOS symptoms/stiffness, KOOS quality of life, EQ-5D and VAS for the intervention group. One patient developed low back pain during the course of the programme. Functional outcomes were equivocal.

Rezende et al. (2017)	195 intervention: 148 (control: 47)	Knee OA Age ≥ 45 years	Parallel group RCT	Orthopaedic surgeons Physiotherapist Dietician Psychologist Social worker Occupational therapists	Class group had six subgroups, named 1,2,3 which had lectures one, two and three months apart either with (A) telephone call or (B) without.	Control: Educational material	Primary: Pain, function, and quality of life (WOMAC, Lequesne, VAS and SF-36). Secondary: Retention and adherence, weight loss and body composition (fat percentage), knee joint and inflammation, pain and function, mobility and HRQL.	17, 52, and 104	WOMAC, WOMAC pain and quality of life improved at 17 weeks. Summary scores obtained for WOMAC, WOMAC pain, VAS, Physical domains (PCS) and SF-36. Patients improved more at 17 weeks than 52. Improved function on Lequesne, TUG, and FTSST in the class group compared with the control. Higher percentage of patients in class group performed regular physical activity.

Khachian et al. (2020)	80 intervention: 40 control:40	Knee OA Age ≥ 18 years	Parallel group RCT	Not reported	Self-management program: OA and treatment, drug management, symptom management, psychological consequences management, pain relief methods, diet, exercise practice. The program covered pain, diet and exercise. The contents of each training session were also provided in pamphlet.	Control: OA self-management booklet plus usual care.	Primary: Self-reported knee pain (KOOS) Secondary: Other symptoms, activities of daily living, sport and recreation function, and quality of life (Knee Injury Osteoarthritis Outcome Score).	8	Significant differences in the mean scores for pain and quality of life after the implementation of the self-management program in the intervention group compared to control group. Self-management programme can improve all outcomes.

da Silva et al. (2015)	41 intervention:19 control:22	Knee OA Age ≥ 18 years	Parallel group RCT	Physiotherapist	Group rehabilitation program prior to randomisation that was self-management program containing information about OA. Educational aspects about knee OA, physical activities weight control and healthy diet, home exercise	Control: group rehabilitation program prior to randomisation. Booster educational information about the disease and how to improve quality of life and function	Primary: Severity of Knee OA (Lequesne algofunctional index). Secondary: General heath and quality of life (SF-36). Performance tests (chair-stand, sit and reach), (timed up and go), and (6-minute walk test).	8	Improvements on Lequesne total score pain and function subdomain, SF-36 physical function and mental health sub domains and performance assessed by chair-stand, TUG, 6MWT for the intervention group compared with control.

2.3.4 Interventions details

The median (IQR) total number of interventions' sessions (Figure 2—2) delivered was 10 (11.8), with the total duration of all sessions being 16.8 (6.4) hours delivered over an eight (6) week period. The median number of sessions delivered each week was two, with their median (range) duration per session being 82 (30-150) minutes (Figure 2—3).

Figure 2—2 Total number of sessions of each study in the intervention arm

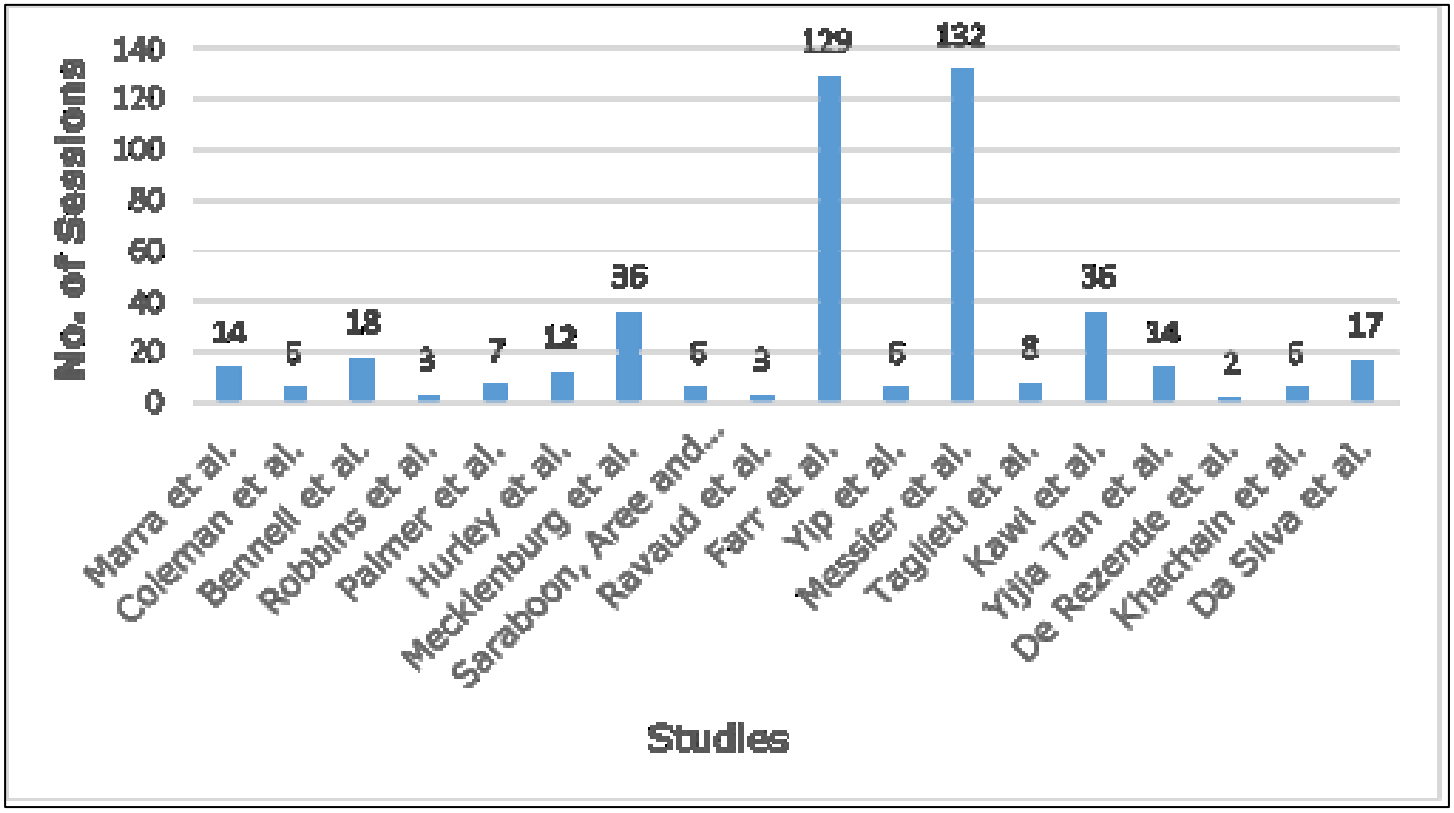
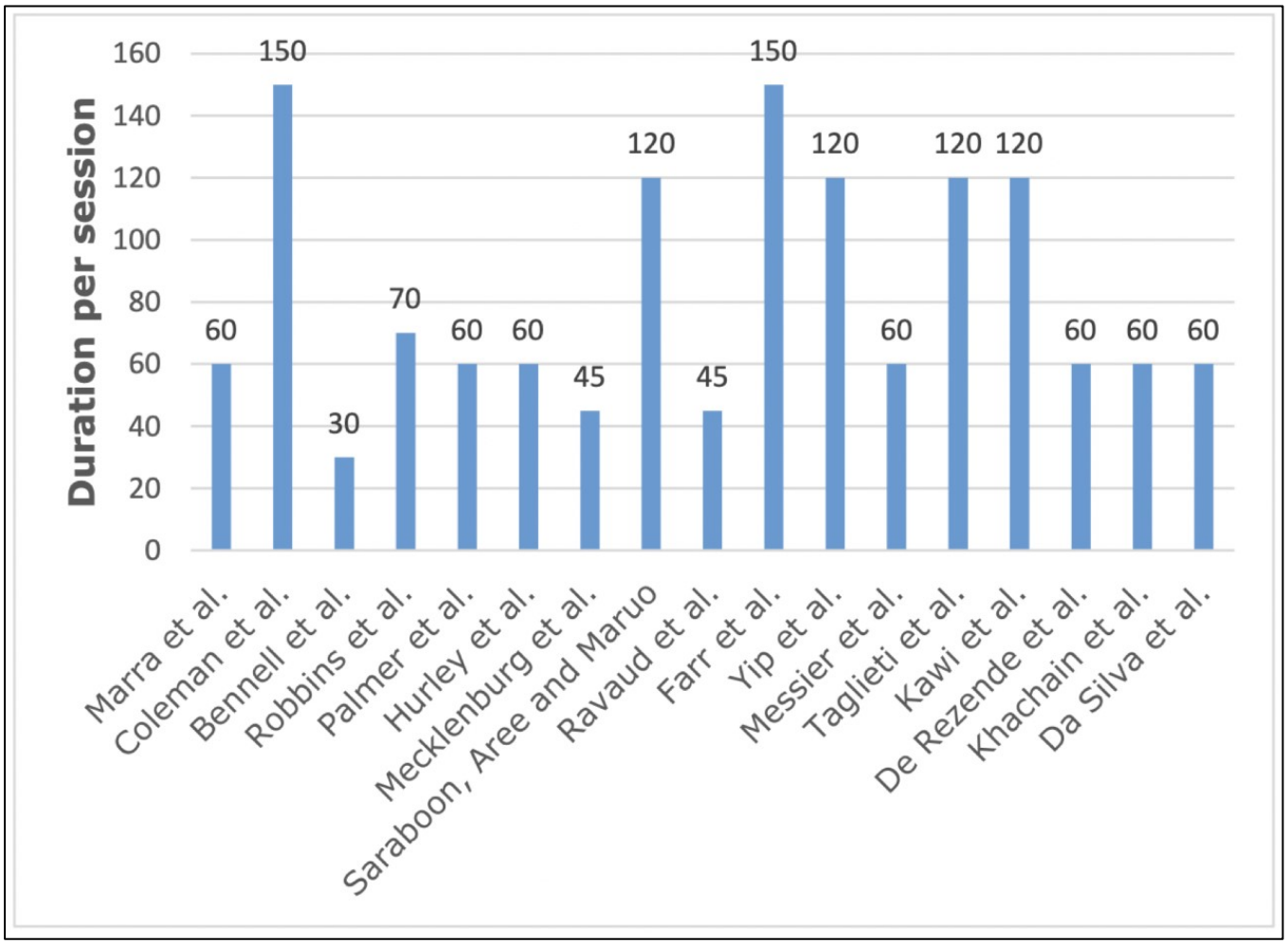


Figure 2—3 Duration per session (minutes) of each treatment visit in the intervention arm



All the studies have provided a brief name of their intervention. In terms of delivery, in ten studies (55%) the interventions were delivered in groups, five (28%) were delivered on the individual level and three (17%) combined both. There were four studies (22%) with interventions delivered online.

All studies (100%) included physical activity, education on OA, and dietary management.The most frequent types of exercises used were strengthening, balance, aerobic, flexibilityand mixed exercise types. The intervention was delivered in a standardised format withoutany tailoring to the individual in 28% of the studies. In most studies (Bennell et al., 2020,Hurley and Walsh, 2012, Kawi et al., 2015, Khachian et al., 2020, Marra et al., 2010, Mecklenburg et al., 2018, Palmer et al., 2010, Rezende et al., 2017, Robbins et al., 2020,Saraboon et al., 2015, Tan et al., 2020), healthcare professionals advised patients to workwith their family members to assist them in diet and exercise (used personal and social networks), utilised behavioural modification, and delivered the psychological intervention.Four studies

used social cognitive theory; two cognitive behavioural therapy, one Acceptance Commitment Therapy, and one social learning theory of Bandura. None of the studies used weight loss surgery, meal replacements, prescription of obesity drugs, or Over the Counter medications. Figure 2—4 demonstrates the proportions of the studies that delivered different components of the intervention.

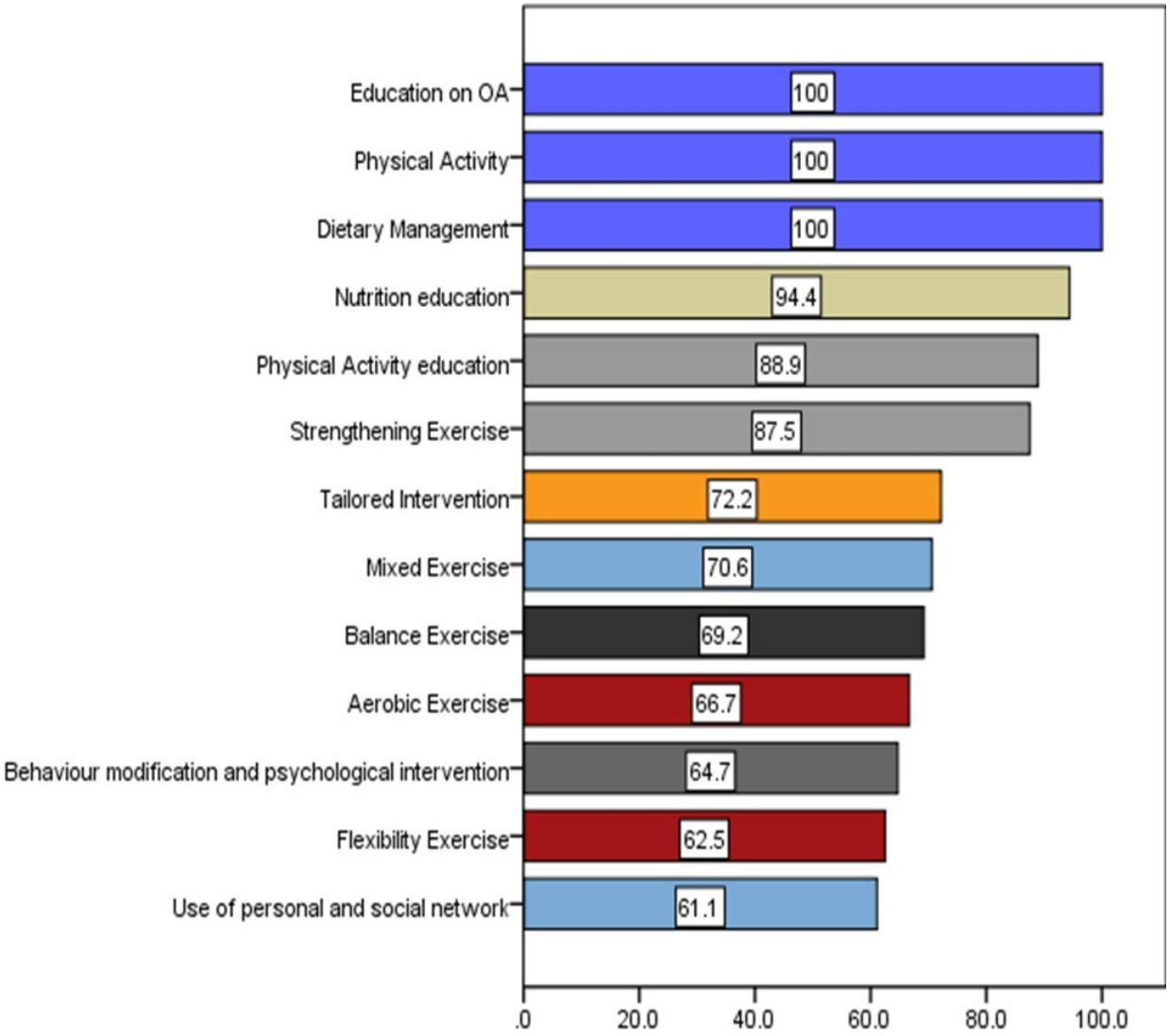


Figure 2—4 Proportion of studies that delivered individual components of intervention

2.3.5 Comparators details

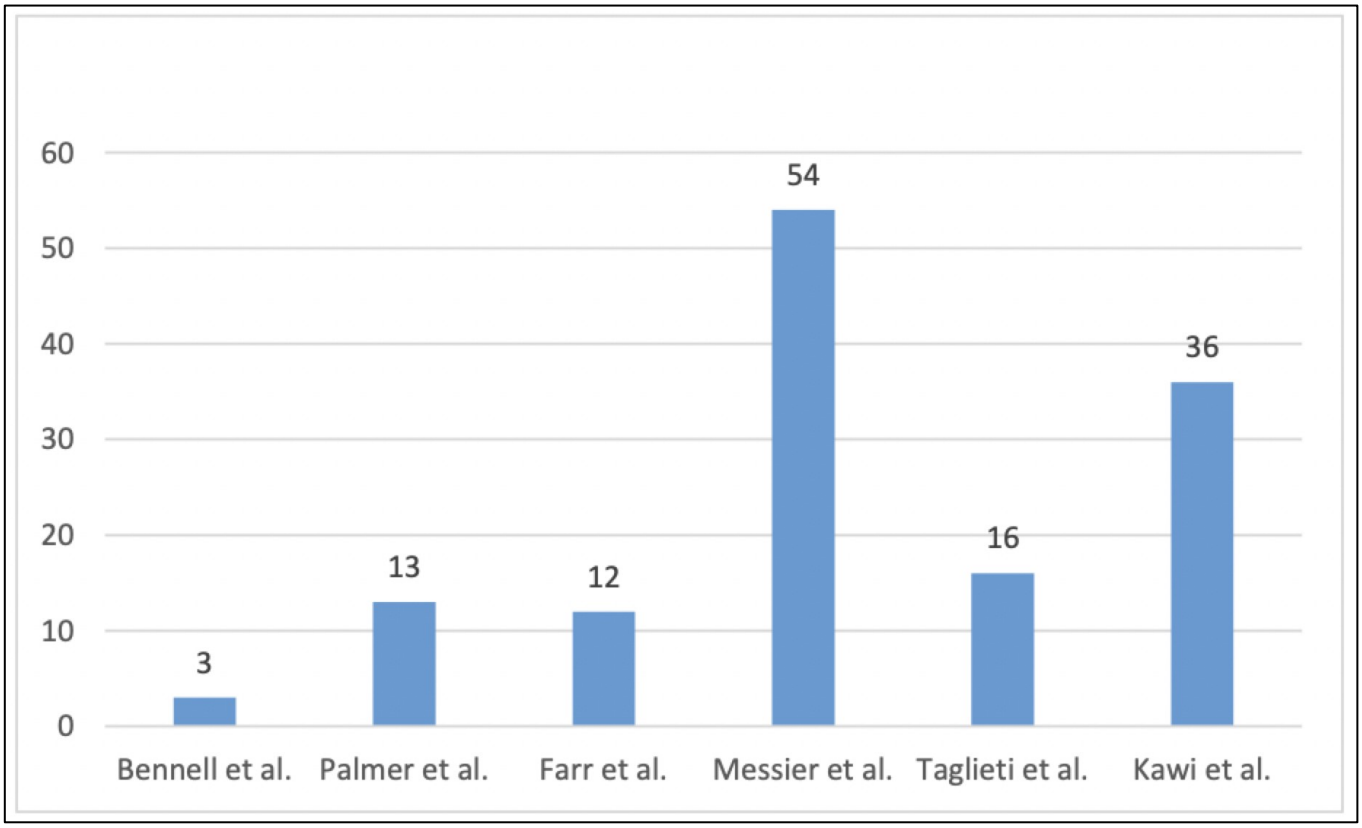
Half of the studies (50%) used usual care as a comparator but often the management options available in usual care were poorly described. Few studies (39%) used educational leaflets/pamphlets on knee OA and six (33%) provided a more detailed intervention. These studies (33%) used online education, TENS plus exercise, self-management (SM) and resistance training (RT), diet, aquatic therapy, and stepping exercise as comparator interventions. The individual components of the comparators and the method of delivery used in each of the six studies can be found below (Table *2—5*)

Table 2—5 Individual components in the six studies

Individual components	**Comparator intervention** (*Author*)					
	Online education (*Bennell et al)*	**TENS plus education and exercise** (*Palmer et al*)	**SM and RT** (*Farr et al.)*	**Diet** (*Messier et al.)*	**Aquatic Therapy** (*Taglieti et al.)*	**Stepping exercise** *(Kawi et al)*
Strengthening Exercise		✓	✓		✓	✓
Balance exercise		✓	✓		✓	
Aerobic exercise					✓	
Mixed exercise		✓	✓		✓	
Flexibility Exercise					✓	
Physical Activity		✓	✓		✓	✓
Dietary management		✓	✓	✓		✓
Personal and social networks		✓	✓			✓
Behaviour Modification			✓	✓		
Nutrition Education	✓	✓	✓	✓		✓
Physical Activity Education	✓	✓	✓			✓
Education on OA	✓	✓	✓			✓

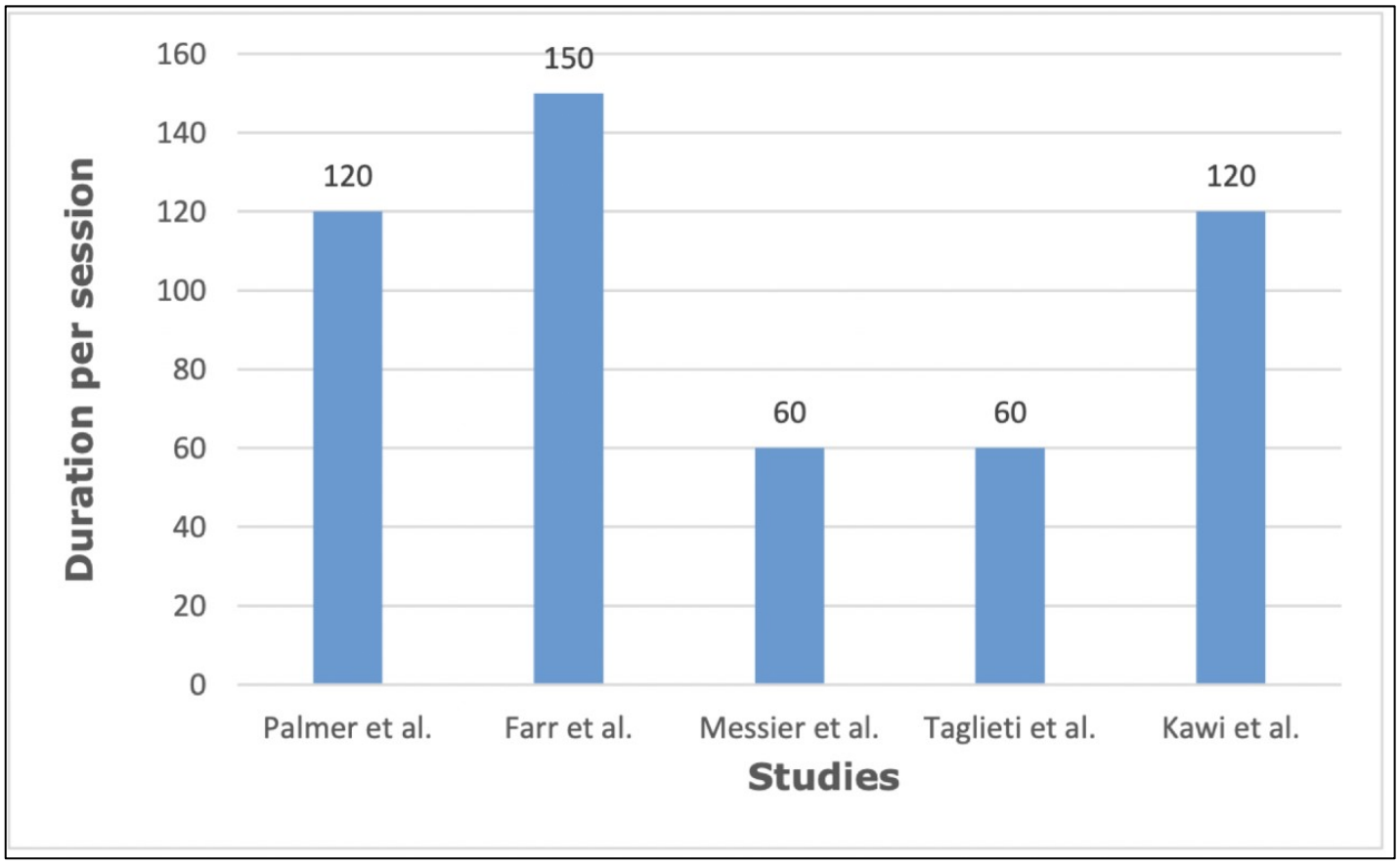
Their median total number of sessions was 14.5 (*Figure 2—5*) with a total duration of sessions being 14 hours, delivered over 10 weeks.

Figure 2—5 Total number of sessions for each study of the comparator



Two sessions were delivered each week with their median duration per session being 2 hours (*Figure 2—6*). Three studies were tailored to the individual and there was only one study, in which the comparator was the group-based intervention.

Figure 2—6 Duration per session (minutes) of each treatment visit in the comparator



2.3.6 Risk of bias

Overall, more than half (55%) of the studies were of high quality (Appendix I). Five studies (28%) had high-risk selection bias. Of these, four did not report how their random sequence was generated or if their treatment assignment was in random order and what method was used (e.g. computer-generated), and one (5%) was quasi-experimental (Kawi et al., 2015). Six studies (33%) did not report any allocation concealment information in their methods. Blinding of the participants and therapists was not possible for any of the studies due to the nature of the intervention. In five studies (28%), the outcome assessor was not blinded. There was a significant imbalance in the sample size of the study arms for one study (5%). With regards to selective outcome reporting, 28% of the studies had a high risk of bias as they neither pre-specified the outcome of the study nor have they selected a valid and reliable scale to measure their outcome. Further details about the proportions of the individual domains of risks of bias are displayed in the summary plot (Appendix II).

2.3.7 Quality of reporting of the trials

The completeness of intervention reporting was higher for the intervention conditions (76%) than for the control conditions (42%). Figure 2—7 displays the quality of reporting (%) of both intervention and control groups combined for each item of the checklist. Tidier summary scores (%) of each trial and the total scores of each item across all trials of both intervention and control groups are present in Table 2—6.

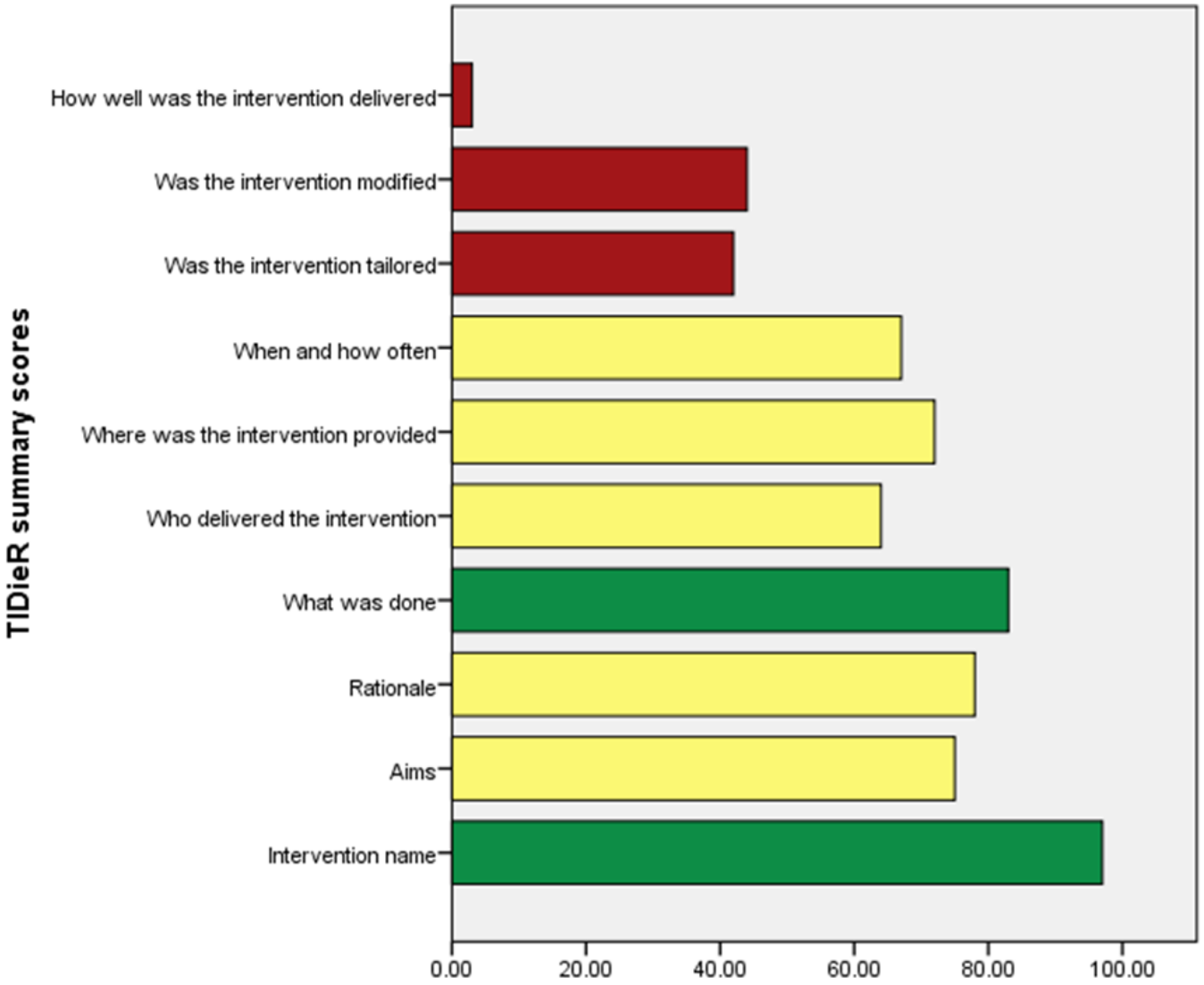


Figure 2—7 TIDieR total scores (%) of each item across all trials

Table 2—6 Total TIDieR scores of all items and summary scores for each trial combining intervention and control group

Item numbers	1	2	3	4	5	6	7	8	9	10	TIDieR summary score (0-20) per study (%)
Marra et al. (2012)	✓	?	?	✓	?	?	?	?	?	×	11 (55)
Coleman et al. (2012)	?	?	?	?	?	?	?	?	?	?	10 (50)
Bennell et al. (2017)	✓	?	?	✓	?	✓	✓	?	?	×	13 (65)
Robbins et al. (2020)	✓	✓	✓	✓	?	✓	✓	×	?	×	14 (70)
Palmer et al. (2014)	✓	✓	✓	✓	✓	✓	✓	✓	×	×	16 (80)
Hurley et al. (2007, 2012)	✓	✓	✓	✓	✓	✓	?	?	?	×	15 (75)
Mecklenburg et al. (2018)	✓	✓	✓	✓	×	×	?	?	✓	×	12 (60)
Saraboon et al. (2015)	✓	?	?	✓	?	?	?	?	×	×	10 (50)
Ravaud et al. (2009)	✓	✓	✓	✓	✓	✓	?	?	?	×	15 (75)
Farr et al. (2010)	✓	✓	✓	✓	✓	✓	✓	×	✓	×	16 (80)
Yip et al. (2008)	✓	?	?	×	?	?	?	×	?	×	8 (40)
Messier et al. (2013)	✓	✓	✓	✓	×	×	✓	×	✓	×	12 (60)
Taglieti et al. (2018)	✓	✓	✓	✓	✓	✓	?	×	×	×	13 (65)
Kawi et al. (2015)	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	17 (85)
Tan et al. (2020)	✓	?	?	×	✓	✓	×	✓	×	×	9 (45)
De Rezende (2013, 2016, 2017)	✓	✓	✓	✓	✓	✓	✓	×	×	×	14 (70)
Khachain et al. (2020)	✓	?	?	?	×	?	×	×	×	×	6 (30)
Da Silva et al. (2015)	✓	?	?	✓	?	?	✓	?	?	×	12 (60)
Total score per item (%)	35 (97)	27 (75)	28 (78)	30 (83)	23 (64)	26 (72)	24 (67)	15 (42)	16 (44)	1 (2)	

Excellent quality of reporting was achieved for the intervention name and what was done items; moderate scores were found for aims and rationale, who delivered the intervention,where, and when, and how often items. Information about the fidelity of delivery (how well was the intervention delivered), modification of the intervention, and tailoring of the intervention items was low (<50). Overall, high quality of reporting was found for three studies, moderate quality for twelve, and low quality of reporting for three studies. *Table 2—7* shows the proportion of included studies using the TIDieR items of included studies that were rated as 'yes' on each TIDieR item and were calculated for the intervention and control groups (separately).

Table 2—7 Number and proportions of achieving a "yes" for each TIDieR item in both intervention and control group

Items	**Intervention Group**	**Control Group**
	(n=18), %	**(n=18), %**
1. Intervention name	100	94
2. Aims	100	50
3. Rationale	100	50
4. What was done	88.9	72
5. Who delivered the intervention	83.3	22
6. Where was the intervention provided	88.9	50
7. When and how often was provided	77.8	50
8. Was the intervention tailored	61.1	11
9. Was the intervention modified	55.6	22
10. How well was the intervention	5.6	0
Mean (SD) score	76 (29.3)	42 (27)
Median (IQR) score	86 (59.7, 100)	50 (22, 50)

2.3.8 Reporting of implementation fidelity

Treatment delivery

A summary table on the level of reporting of implementation fidelity in treatment delivery is displayed in Table 2—8. Overall, only 17.6% of the items were presented sufficiently (++), 25.5% were presented insufficiently (+), and 56.87% items were absent (A). Eleven studies (64.7%) insufficiently presented (+) the method to ensure that the dose of the intervention is delivered as specified, four (23.5%) presented that item sufficiently (++), and in two (11.8%) studies that item was absent. With regards to the method to ensure that the content of the intervention is delivered as specified, ten (58.8%) studies presented that item insufficiently (+), four (23.5%) sufficiently (++), and in three (17.6%) that item was absent (A). In nine studies (52.9%) the mechanism to assess if the provider adhered to the intervention was absent, in five (29.4%) it was presented sufficiently (++) and in three (17.6%) presented insufficiently (+). Eleven (64.7%) studies did not provide information (A) about the assessment of nonspecific treatment effects, three (17.6%) provided this information sufficiently (++) and three (17.6%) provided this information insufficiently (+). Nine studies (52.9%) did not use a treatment manual (A), three (17.6%) used, and five (29.4%) presented information insufficiently (+). In fourteen (82.4%) studies, there was no plan to assess if the active ingredients of the intervention were delivered (A), and in three (17.6%) studies that information was presented insufficiently. Information to assess if the prescribed components were delivered was absent for fourteen (82.4%) studies, presented sufficiently for two (11.8%) and presented insufficiently for one (5.9%). Information regarding the contamination between conditions was absent for eight (47.1%) studies, presented sufficiently for 6 (35.3%) and presented insufficiently for 3 (17.6%). None of the studies (100%) specified treatment fidelity (A).

Table 2—8. Level of reporting of implementation fidelity strategies in included studies: treatment delivery

Author (year)	1. Method to ensure that the dose of the intervention is delivered as specified	2. Method to ensure that the content of the intervention is delivered as specified	3. Mechanism to assess if the provider adhered to the intervention plan or in the case of computer delivered interventions, method to assess participants' contact with the information	4. Assessment of non-specific treatment effects	5. Use of treatment manual	6. There is a plan for the assessment of whether the active ingredients were delivered	7. There is a plan for the assessment of whether or not proscribed components were delivered	8. There is a plan for how the contamination between conditions will be prevented	9. There is a priori specification of treatment fidelity	Comments
Marra et al. (2012)	+	+	A	A	A	A	++	+	A	Contamination between conditions was prevented through clusters.
Coleman et al. 2012	+	+	A	A	++	+	+	A	A	Treatment manual was provided. Attendance sessions were recorded. Fidelity was maintained but not measured.

Bennell et al. (2017)	+	++	++	++	++	A	A	A	A	Treatment manual was provided; weekly meetings between researchers and those delivering the interventions; separate qualitative component was published to assess the participants' experience.
Robbins et al. 2020	+	+	A	+	A	A	A	A	A	Use of a treatment protocol, paper acknowledged that they did not assess treatment adherence, compliance, and fidelity.
Palmer et al. 2014	+	+	++	A	+	A	++	++	A	Used a treatment protocol. Measured exercise adherence. TENS machine recordings were checked at the end; participants are asked to log frequency of use.
Hurley and Walsh 2012	A	A	A	++	A	A	A	++	A	Cluster RCT prevented contamination. Assessed non-specific treatment effects

Mecklenburg	++	++	++	A	A	A	A	++	A	Bluetooth sensors strapped to participants' legs to monitor activity was used; personal coach was involved for accountability; email reminders are sent.
Saraboon et al. 2015	++	+	+	A	+	A	A	+	A	Participants were asked to accomplish a food diary; home visits were done; implementation guide was used; evaluation and feedback were completed.
Ravaud et al. 2009	+	+	+	++	++	+	A	++	A	Guidelines were provided to physicians; clear description of the content was included on the case report form, rheumatologists had to use a pre-printed data collection form following algorithms, use similar language and explanations at each step of the programme, and provide specific leaflets to patients; An independent data collector evaluated patients' satisfaction and knowledge during a phone interview.

Farr et al. 2010	++	++	++	A	A	A	A	++	A	Participants completed training logs during all sessions and reported sets, repetitions, and loads for each exercise. Certified physical trainers supervised all RT sessions, monitored progression, and tested participants following standard protocols; participants wore accelerators.
Yip et al. 2008	+	A	A	+	A	A	A	A	A	No data to share, most information was absent.
Messier et al. 2013	++	++	++	A	A	+	A	++	A	Unclear if they used treatment manual. Adherence data were reviewed regularly to identify participants who needed additional counselling. Participants In interventions monitored themselves by completing daily logs.

De Rezende et al., 2016	+	+	+	A	+	A	A	A	A	Patients were reminded repeatedly to watch the DVD and/ or read the material; to exercise at least 3 times a week; and to change their social, occupational and dietary habits
Khachian et al., 2020	A	A	A	A	A	A	A	A	A	No treatment protocol was used. Implementation fidelity checklists and site visits missing.
Kawi et al., 2015	A	+	A	+	+	A	A	+	A	Use of a treatment protocol but details of the intervention not provided.
Da Silva et al., 2015	+	+	A	A	+	A	A	A	A	Use of a treatment protocol.
Tagglieti et al., 2018	+	+	A	A	A	A	A	A	A	Use of a treatment protocol for the exercise.

Treatment Receipt

With regards to the treatment receipt, a total of ninety items were assessed (Table 2—9). Of those, 35.6% were absent (A), 31.1% were insufficiently reported (+) and 33.3% were reported sufficiently (++). Eight studies (44%) sufficiently (++) provided a strategy to assess the degree to which the participants understood the intervention, six (33.3%) insufficiently (+) provided that strategy, and in four studies (22.2%) this information was absent (A). Eleven studies (61.1%), sufficiently (++) specified the strategies to improve participant comprehension of the interventions, five (27.8%) insufficiently specified the strategies and in two studies (11.1%) this information was absent (A). Three studies (16.7%) sufficiently assessed participants' ability to perform the intervention skills (++), nine studies (50%) insufficiently (+) reported this information and in six (33.3%) this information was absent (A). Seven studies (38.9%) sufficiently (++) specified the strategies used to improve participant performance of the interventions, eight (44.4%) insufficiently (+) specified those and in three (16.7%) this information was absent (A). Seventeen studies (94.4%) did not consider multicultural factors in the development and delivery of the intervention at all (A), and only one study (5.6%) sufficiently reported and considered the factors (++).

Author (year)	Assessment of the degree to which participants understood the intervention	Specification of strategies used to improve participant comprehension of the interventions	Assessment of the participants' ability to perform the intervention skills	Specification of strategies used to improve participant performance of the interventions	Consideration of multicultural factors in the development and delivery of the intervention	Comments
Marra et al. (2012)	A	++	++	+	A	Education regarding counselling on the symptoms and other aspects of knee OA. Exercises were shown during the class by the physiotherapist. They were supervised by a rehabilitation assistant and the physiotherapist was available if needed. At the end of weeks 3 and 6, the patients were reassessed by the physiotherapist and the participant's exercise recommendations were adjusted as needed.
Coleman et al. 2012	A	+	A	+	A	Participants are given printed information relevant to the course component discussed each week.
Bennell et al. (2017)	++	++	+	++	A	Participants received 3 Internet-delivered treatments. - The first was educational material about exercise and physical activity, pain management, emotions, healthy eating, complementary therapies, and medications (www.arthritisaustralia.com.au). Participants were encouraged to access the material at their leisure.

						- The second was an interactive automated program. Participants were asked to complete eight 35- to 45-minute modules. - The third was 7 Skype sessions with a physiotherapist over 12 weeks. - Exercise progression was provided by varying the exercises, repetitions, load, or difficulty to approximate a 10-repetition maximum level and a self-rated effort level of at least 5 out of 10 (hard) on a modified Borg Rating of Perceived Exertion scale. - Participants were provided with instructions, video demonstrations, and equipment (such as resistance bands and ankle weights). - They also were encouraged to increase physical activity levels, received written information about how to do so, and were given the option of using a pedometer for motivation (provided at no cost).
Robbins et al. 2020	+	+	A	A	A	The control group received educational leaflets outlining self-management measures for knee OA and were encouraged to access the Pain website.
Palmer et al. 2014	++	++	++	++	A	TENS instruction comprised a 30-minute appointment during which patients were also assessed for competency to self-administer.

Hurley and Walsh 2012	++	++	+	+	A	All written and verbal instructions were standardised as far as possible. Patients were allowed to ask questions and received further instruction as required to ensure adequate understanding. Participants had supervised sessions Physiotherapist facilitated a discussion on a specific topic, advising and suggesting simple coping strategies. Then, for 35–40minutes each participant performed a simple individualised exercise regimen to address their disabilities and progressed this as they improved.

Mecklenburg et al. 2018	++	++	+	++	A	Participants received a tablet with a Health application installed, and two custom Bluetooth sensors with straps to be used on the upper and lower leg during the in-app exercise therapy. Participants were assigned a personal coach that provided support and accountability throughout the program and were placed in a team to provide peer support through a discussion feed within the app. Participants were set the goal of completing 3 sessions of sensor-guided exercise therapy, reading one to two education articles, logging their symptoms at least twice, performing cognitive behavioural therapy (CBT; subset of weeks only), working at weight loss and tracking at least three 30-minute sessions of aerobic activities.
Saraboon et al. 2015	++	++	++	++	A	The researcher provided a health education program aimed at enhancing knowledge and illness representation of OA knee through lectures. A group activity was conducted to facilitate participants to share their experience, perception of OA knee, and health practice. Participants were given OA knee booklets and video compact discs to OA knee information and positive health practices

Through lecture, group discussion, and food model demonstrations, a nutritionist provided comprehensive information on diet. The participants were also instructed how to select good foods, set their own daily menus properly, and calculate calorie intake.

A brisk walking exercise was introduced to participants. The participants were instructed how to perform a brisk walking exercise, and then the participants did a return demonstration to validate they understood and could perform the exercise correctly.

Ravaud et al. 2009	++	++	A	++	A	To improve patients' adherence, our theoretical background was as follows. - The first visit aimed at informing patients about the disease and treatment. - The next two visits focused on only one component each (exercise and weight loss). This focus allowed for a simplification of the message to improve patients' comprehension and recall of information. - Tailored counselling of patients, the exercise programme took into account patients' preferences, and the strategy for losing or maintaining weight varied according to patients' readiness to change. - specific documents provided to patients included information on osteoarthritis and a booklet to record weight and physical activities each week.
Farr et al. 2010	+	+	+	+	A	Participants met with certified physical trainers. Supervised, small-group sessions were held to improve adherence. Classroom sessions in which participants completed SM education modules addressing an overview of OA, general exercise principles and PA recommendations, stress management, foot care, pain management, analgesic and anti-inflammatory medications,

						nutrition for health, coping mechanisms, communication with health care providers, and healthy lifestyle practices.
Yip et al. 2008	A	+	+	+	++	Participants who were eligible and willing to participate in the study were recruited on voluntary basis. The patients were given detailed information about study procedures. The team scaled up the focus on goal-directed exercise components relevant to the group's lifestyle habit. Before each class session, the tutor asked each participant to set an action plan on the three types of exercise. The individual action plan was promoted and reinforced weekly during the course. The content of the ASMP with added in exercise components was pre-tested and piloted to make sure that the content and selected exercise were culturally acceptable and relevant to the osteoarthritis. Verbal persuasion, social inter-actions during the programme and group-mediated learning sessions.
Messier et al. 2013	A	A	+	+	A	Adherence data were reviewed regularly to identify participants who needed additional counselling

Kawi et al. 2014	+	++	+	++	A	Participants received written instructions and were monitored by at least two trainers and supervised by one of the researchers. Trainers (health sciences students) facilitated **integrity of the intervention.** All participants received an email to register for the online SM program that was hosted in a website. This is for posting on the discussion boards or communicating with online NCOA-trained workshop facilitators for content questions. Pre-set weekly modules with topics were covered An interactive discussion board was provided to encourage group support while individualized tailored care is enhanced through personalized tools.

Khachian et al. 2019	++	++	A	+	A	The intervention group received comprised one 60 min education session each week. The program covered the management of pain, proper diet, and exercise During the sessions, to engage them through question and answer, patients were encouraged to discuss their experiences of the factors that contributed to the improvement or worsening of their pain and other illness-related problems. The contents of each training session were also provided in a pamphlet, and patients were requested to practice at home. For the intervention group the researcher presented information about self-management topics including illness and treatment, drug management, symptom management, psychosocial consequences management, pain relief methods, proper dietary education, and instruction in exercise practices. The researcher followed up the patients through a follow-up card and weekly phone call
Taglietti et al. 2018	+	+	+	+	A	The classes were weekly (total of eight), lasting 2hours and were given at the Primary Health Care Unit. This group also received home knee osteoarthritis exercise guidelines for practice two to three times a week, which included warm-up, self-stretching, isometric and dynamic exercises, proprioceptive and

						functional exercises of the lower limbs, and cool down.
da Silva et al. 2015	+	++	A	A	A	Prior to randomization, the patients participated in a self-management program that consisted of a lecture containing general orientation about osteoarthritis. CG participants received booster educational information about the disease and how to improve quality of life and function through leaflets. The intervention group received educational aspects about KOA

Uchoa de Rezende et al. 2016	++	++	+	++	A	The first day comprised lectures. Each professional team had a lecture of 30 to 40minutes (orthopaedic surgeons, psychology, physical therapy, occupational therapy, physical fitness, and social workers) or up to 80 minutes (nutritionist). During the workshops, the physical therapy team taught the patients the exercise series presented in the booklet and in the DVD, which was to be conducted at least 3 times a week. The medical team closed the program by quizzing patients on the definition, causes and management of OA, and recalling highlights of each team's presentations.
Tan et al. 2020	+	A	A	A	A	All patients would receive the education and physical exercise components.

Table 2—9 Level of reporting of implementation fidelity strategies in included studies: treatment receipt

2.3.9 Narrative synthesis of the non-meta-analysed studies

Study characteristics

Six studies were included in the narrative synthesis of the non-meta-analysed studies. These were published from 2012 to 2020 and conducted in Canada, UK, Brazil, USA, Singapore, and Thailand. Two were delivered in primary care, two in secondary care, and two in the community. Three were parallel group RCTs, one was feasibility RCT, one was cluster RCT, and one was quasi-experimental. Three (50%) were single centre and three (50%) were multi centre. One study (Saraboon et al., 2015) did not report the funding source and whether informed consent was obtained from participants. All studies reported the eligibility criteria of the population. Three studies (50%) used the ACR criteria for knee OA, one used grade ≥2 KL classification criteria, one physician diagnosis of OA, and one knee pain on most days of the previous month. All studies obtained ethical approval. Participant characteristics of the non-meta-analysed studies are displayed in Table 2—10.

Review of participant numbers at each stage of recruitment of the non-meta-analysed studies: In total, 1457 people with knee pain due to OA were approached to take part, of which 799 met the inclusion criteria. The number excluded was 811 with 143 declining to participate. Overall, 539 patients with knee OA and mean age of 63.8 years (SD 3.3) and body mass index of 30.2 (SD 5) kg/m^2 were randomised into groups. Of those, 72 have dropped out. Information about the number of patients excluded and declined to participate was not provided by Kawi et al. (2015) and Saraboon et al. (2015). Further details of the participants' characteristics for each study are displayed in Table 2-10. The final frameworkof narrative synthesis developed providing the features and the results of the non-meta-analysed studies is in Table 2—11.

Table 2—10 Participant characteristics for the non-meta-analysed studies of each study

Author (year)	Sample size (n)	Age mean (SD)	BMI mean (SD) kg/m^2	females %	Inclusion criteria
Marra et al. (2012)	139	61.8 (8.3)	31.1 (12.3)	57	Knee pain on most days of the previous moth
Palmer et al. (2014)	224	61.4 (10.5)	29.5 (9.2)	62.7	ACR criteria for knee osteoarthritis
Saraboon et al. (2015)	80	67.4 (6.8)	26.4 (2.3)	92.5	ACR criteria for knee osteoarthritis
Taglietti et al. (2018)	60	68 (6.3)	29.8 (1)	68.2	ACR criteria for knee osteoarthritis
Kawi et al. (2015)	16	60.9	34.1	100	Physician or doctor-diagnosed knee OA
Tan et al. (2020)	20	63.8 (8.3)	Not available	85	KL grading method

Table 2—11 Study and intervention characteristics of the non-meta-analysed studies

Author (Year)	Sample Size (intervention, control)	Participant characteristic	Design	Intervention delivery	Intervention	Comparator	Outcome (measures)	Time points (week)	Results
Marra et al. 2012	139 intervention:73 control: 66	Knee pain Age ≥ 50 years	Cluster RCT	Pharmacist Physician Physiotherapist	Medication review Education Nutrition Individualised home-exercise programme	Control group: Pamphlet on knee OA by Arthritis Society plus usual care	Primary: Quality of care for OA (Arthritis Foundation quality indicators). Secondary: Knee pain and function (WOMAC), lower extremity function (LEFS), generic quality of life (PAT-5D), and the Health Utilities Index Mark 3 (HUI-3)	13 and 26	WOMAC pain, function, PAT-5D, LEFS, and HUI-3 improved in the intervention group compared to control group at 13 and 26 weeks
Palmer et al. 2014	224 intervention A:73 intervention B:74 intervention C:77	Knee OA Age ≥ 18 years	Parallel group RCT	Physiotherapist	Arm A: active Tens and knee group (OA education, exercise, weight loss)	Arm B: Sham Tens and knee group Arm C: Knee group	Primary: Physical function (WOMAC). Secondary: Pain, stiffness and total scores (WOMAC subscales).	3, 6, 12 and 24	WOMAC function and total scores improved over time for all arms. No differences between trial arms. Improvements maintained at 24 weeks.

Saraboon et al. 2015	80 intervention:40 control: 40	Knee pain Age ≥ 50 years	Parallel group RCT	Nutritionist	Education programme about OA. Weight reduction programme and exercise either individually or in groups and home visits.	Control: Knee OA booklet and video compact disk	Primary: Knowledge about OA (10 true/false questions). Secondary: Illness representation of OA knee (0-10 response scale), health outcomes in terms of health behaviours (health behaviour questionnaire), knee pain (NRS), ROM (goniometer), body weight, movement ability (TUG).	8	OA knowledge, illness representation, health behaviour, and ROM, improved in the intervention group compared to control. Mean scores for knee pain and body weight were lower in the intervention group than in the control.
Kawi et al. 2015	16 intervention A:8intervention B:8	Knee OA Age ≥ 50 years	Pilot quasi experimental	Physiotherapist Nurses	Arm A: Progressive walking and online SM program (duration of thewalking sessions was progressed,	Arm B: Progressive stepping + online SM program (height of the steps was progressed)	Primary: Knowledge, skills, behaviours, and confidence of individuals in self-managing their chronic illness (PAM), change in activation scores	6 and 26	Activation scores to SM were significantly higher after intervention in all participants and when evaluated according to exercise groups.

Tan et al. 2020	20 intervention: 10 control:10	Knee pain Age ≥ 45 years	Feasibility RCT	Orthopaedic surgeons Physiotherapist Dietician Psychologist Social worker	Assessment and education exercise therapy Nutrition and dietetics Psychological support	Control: Referral to the outpatient physiotherapist. Lifestyle modifications and exercise therapy.	Primary: Symptoms, pain, function, (daily living), function (sports, recreational activity) and quality of life (KOOS). Secondary Pain, symptoms, function (KOOS), quality of life (EQ-5D-5L), functional assessment (TUG), BMI, psychological related outcomes(PEG, PHQ-4), diet and adverse events	12	Improvements in KOOS, KOOS symptoms/stiffness, KOOS quality of life, EQ-5D and VAS for the intervention group. One patient developed low back pain duringthe course of the programme. Functional outcomes were equivocal.
Taglietti et al. (2018)	60 Intervention A: 29 Intervention B: 31	Knee pain Age > 60	Parallel group RCT	Physician, pharmacist, nurse, nutritionist, psychologist, physiotherapist, and physical educator.	Physical Activity Exercise Hydrotherapy Education	Aquatic therapy programme	Patient education programme	8 and 13	Aquatic exercises, when compared to patient-education, were superior in improving function and pain in individuals with knee OA.

Synthesis

The aforementioned studies could not be included in the meta-analysis due to the following reasons; two studies reported only baseline data (Marra et al., 2010, Saraboon et al., 2015), two reported the median (IQR) (Tan et al., 2020) and had three intervention arms (Palmer et al., 2010), one had hydrotherapy as the main intervention arm (Taglietti et al., 2018), and one was quasi-experimental and did not report any pain outcomes (Kawi et al., 2015). Two of those studies (Kawi et al., 2015, Saraboon et al., 2015) had high risk of bias and did not consider pain as the primary outcome as they reported the activation scores on self-management and OA knowledge/ illness representation of OA. Three studies reported significant improvement in pain outcome measures (Marra et al., 2010, Palmer et al., 2010, Tan et al., 2020) when the outcome was measured in time-points close to week 13 which we considered as the primary time-point for the meta analysis.

2.3.10 Adverse Effects

Only four studies reported adverse effects of the identified studies (Table 2—12).

Table 2—12 List of the side effects of the included studies

Author (year)	Intervention	Control	Comments
Bennell et al. (2017)	Adverse events during treatment (26) • Increased knee pain (15/65) • Muscle cramping/ soreness (5/65) • Pain in other area (5/65) • Swelling (1/65) Participants reporting adverse events during follow-up (5/64) • Increased knee pain (3/64) • Pain in other region (2/64)	Adverse events during treatment (3/67) • Increased knee pain (3) Adverse events during follow-up (6/70) • Increased knee pain (2) • Muscle cramping (2) • Pain in other region (2)	During treatment, more participants in the intervention group (n= 22) than the control group (n=3) reported adverse events. Adverse effects of treatment (any problem believed by the participant to be caused by treatment and lasting ≥2 days and/or requiring medication or treatment) and co-interventions were recorded via log-books during the first 3 months and an online survey at 3, 6, and 9 months. Adverse events were minor, with increased knee pain being most common in both groups (15 and 3 events, respectively).

Robbins et al. (2020)	Ten participants reported a total of 13 adverse events: • pain exacerbation related to the strengthening exercises (7) • related to the diet program (6) which included food intolerances (2) and mild gastrointestinal reactions (4)	No adverse effects reported	No serious adverse events were observed. All adverse events were reported to the sponsor and ethics committee.
Tan et al. (2020)	(1) Patient developed concurrent back pain during the course of the program. • Low back pain was exacerbated during the intervention.	One patient in the control arm who deteriorated was subsequently diagnosed with spontaneous osteonecrosis of the knee and underwent knee arthroplasty.	Assessment by an independent physiotherapist deemed that the exercises prescribed were unlikely to cause the exacerbation. The back exacerbation was treated successfully with physiotherapy and analgesia.
Messier et al. (2013)			Non-serious

2.3.11 Meta-analysis

This meta-analysis examined the overall efficacy of complex interventions comprising patient education, exercise, and weight loss advice with or without any other single non- pharmacological intervention on four outcomes including pain, physical function, anxiety/depression, and quality of life.

Overall effects of the intervention of all outcomes: 12 studies were included in the quantitative synthesis. The primary time point selected was thirteen weeks post- intervention as this was the most commonly reported time-point (Figure 2—7).

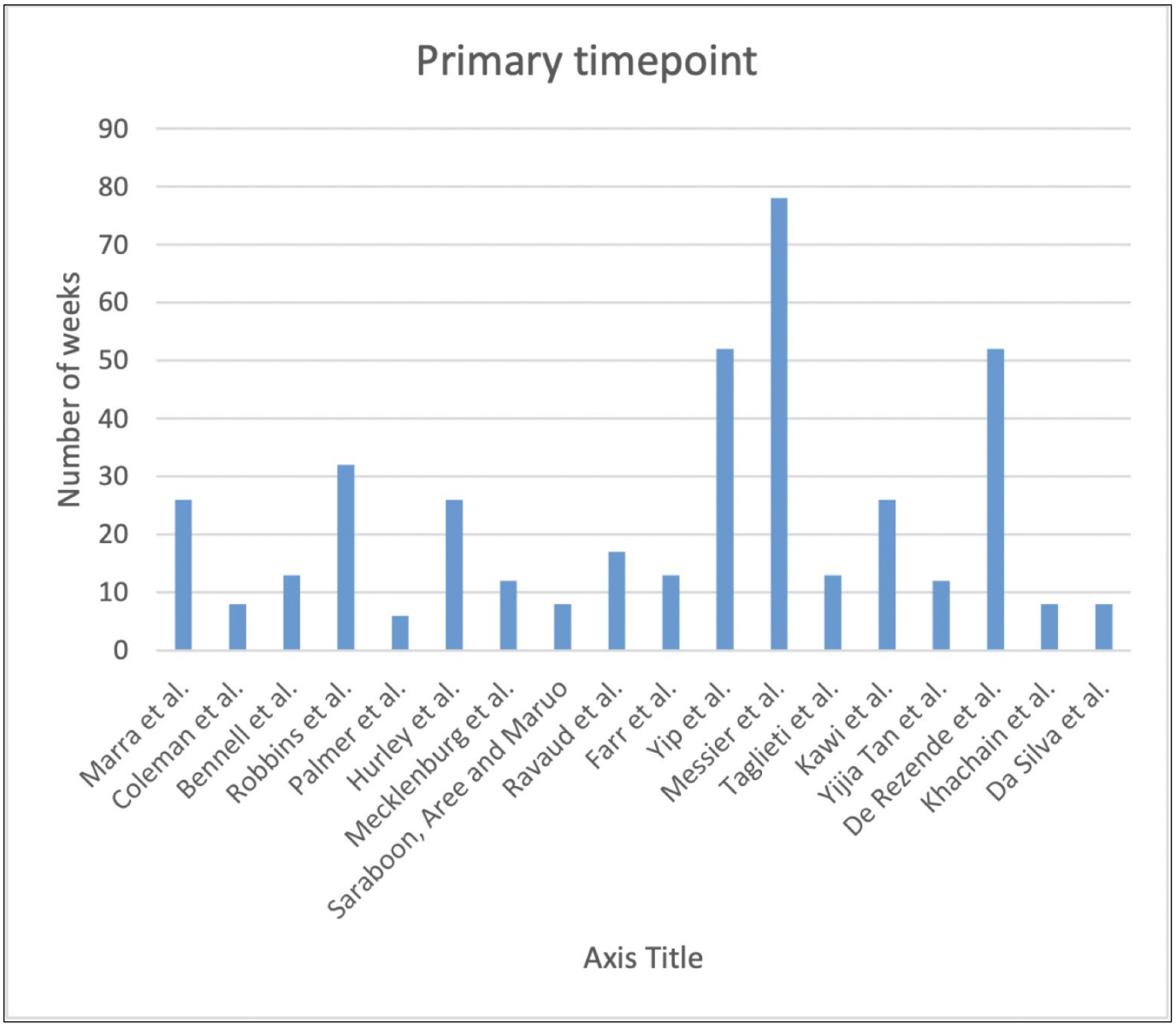


Figure 2—7 Range of time-points of the studies

Figure 2—8 shows that complex interventions for OA produce significant moderate benefit (p=0.00) for pain relief ES (-0.47, 95% CI -0.77, -0.16). Seven studies investigated the effects of complex interventions on physical function (Figure 2—9) and reported reduced risk of physical function impairment with moderate benefit overall ES (-0.49, 95% CI -0.72, -0.25). Effects on anxiety/depression were not pooled as only two studies provided data. For the quality of life, two studies were included in the meta-analysis (Figure 2—10) which demonstrated a large ES (2.10, 95% C 1.40, 2.80). These data are comparing baseline and week 13 outcomes.

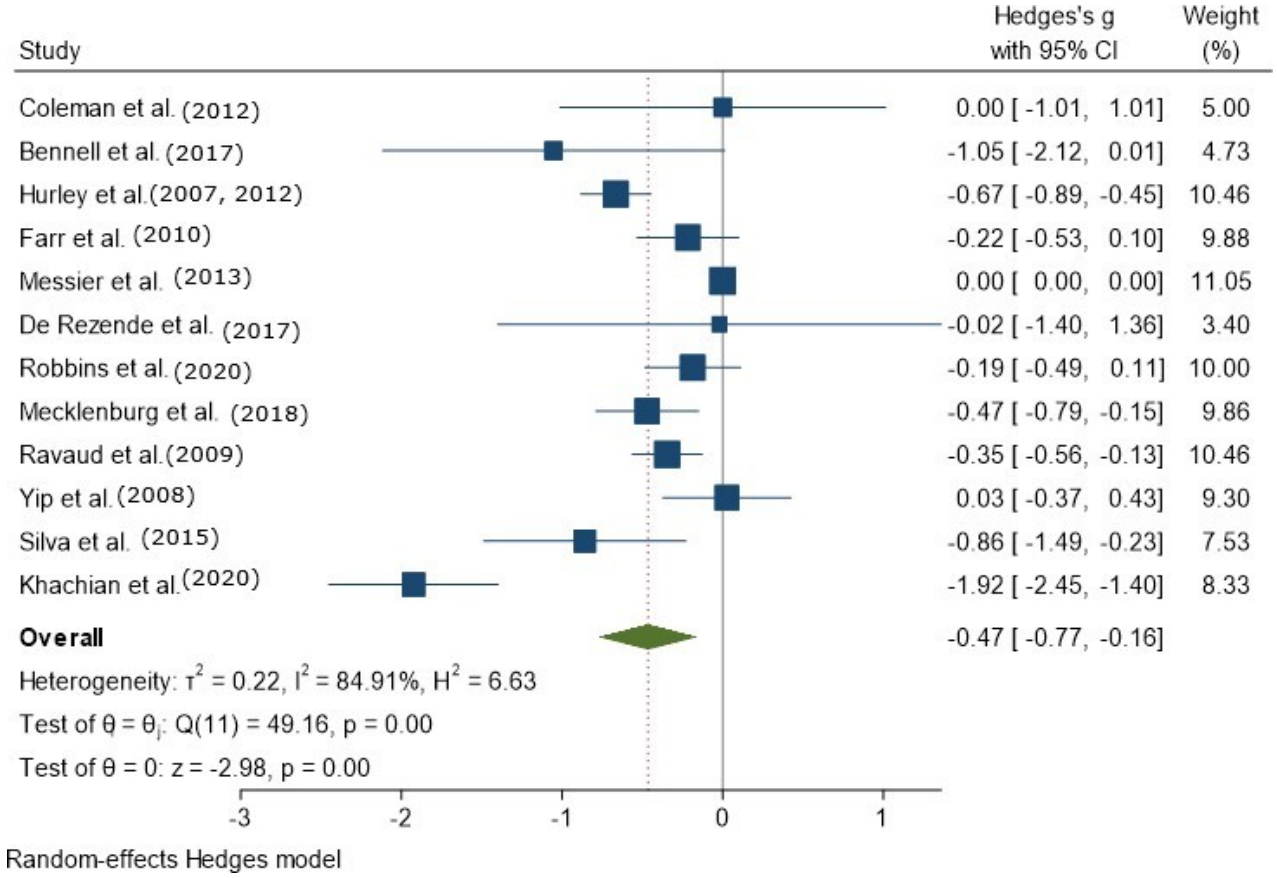


Figure 2—8 Forest plot depicting standardised effect sizes for pain

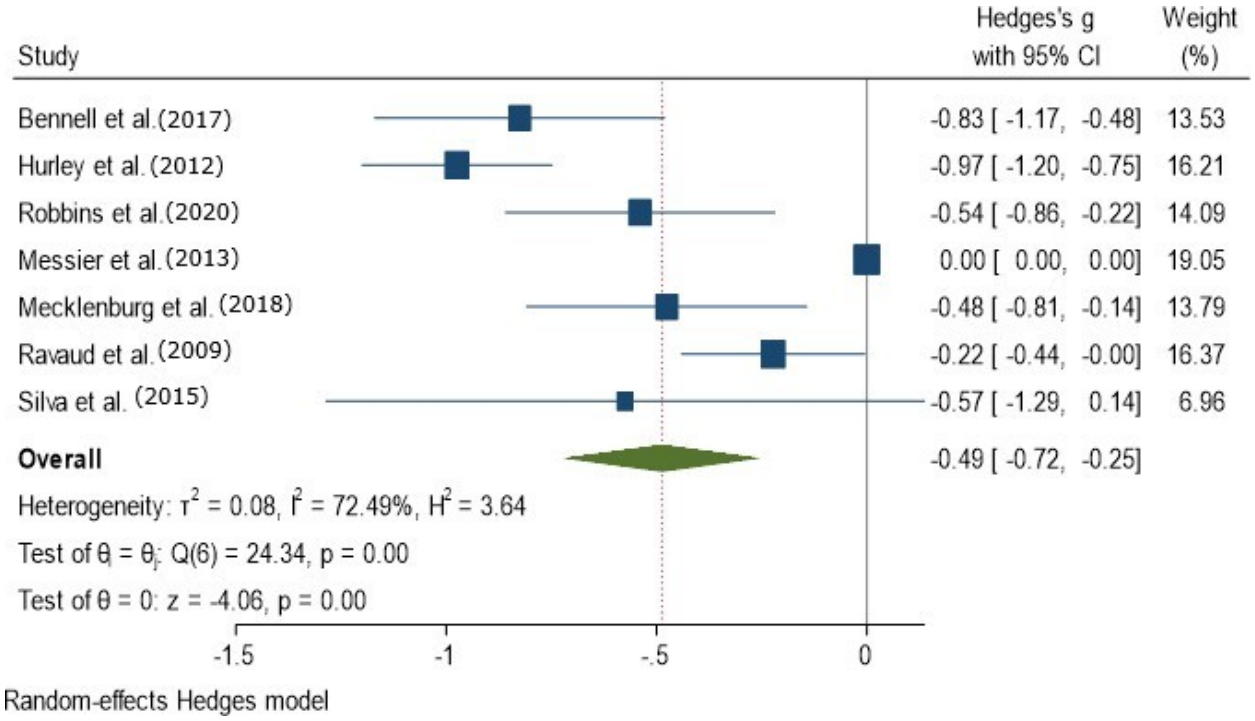


Figure 2—9 Forest plot depicting standardised effect sizes for physical function

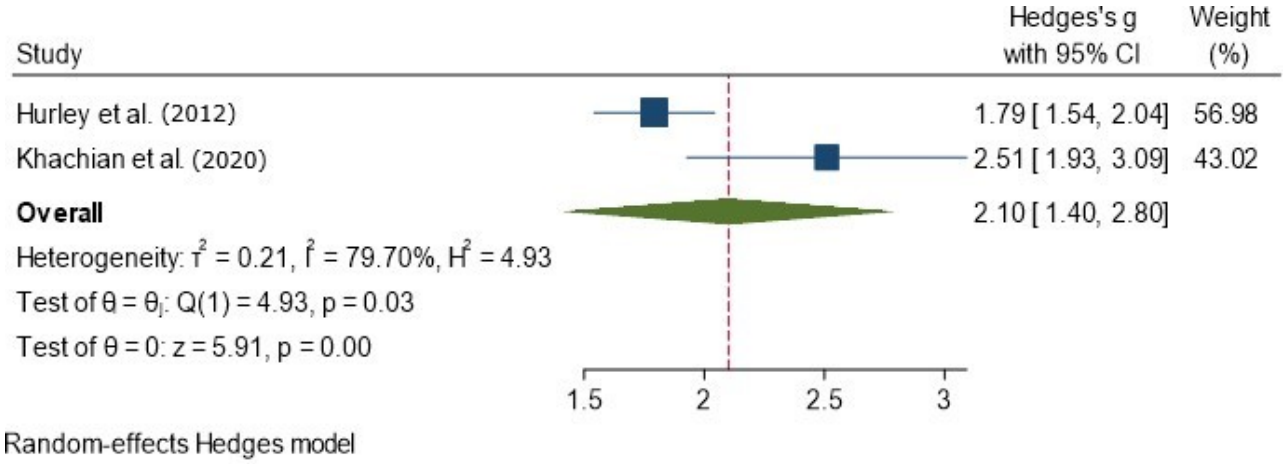


Figure 2—10 Forest plot depicting standardised effect sizes for quality of life

Heterogeneity: Substantial heterogeneity was detected. The included studies varied in terms of participant characteristics such as age, gender, BMI, and criteria to classify knee OA differed. Moreover, as previously shown in Table 2—4, studies differed in terms of intervention delivery, interventions' details, comparators, outcomes, and time points. The included studies were also different in terms of their methodological quality. Quality of reporting of studies' interventions (TIDieR summary scores per study and item across studies) also varied. High statistical heterogeneity was found for pain (I^2= 84.91%), moderate for physical function (I^2=72.49%), and high for the quality of life (I^2= 79.70%). Variation in intervention effects is therefore present. For this reason, investigation of statistical heterogeneity was further conducted by performing subgroup analyses.

Outlier and publication bias of all outcomes: In the observed funnel plot for pain (Figure 2—11) three outliers were detected. The evidence was symmetrically distributed for pain graphically displaying a "funnel shape" plot with no publication bias. As there were more than ten studies included in the analysis, Egger's test was used to test for funnel plot asymmetry for pain (H0= beta1=zero; no small study effects beta1= -0.64, SE of beta1 = 0.971, z=-0.66 prob>= 0.5107). Potential for publication bias was not detected (p>0.05).

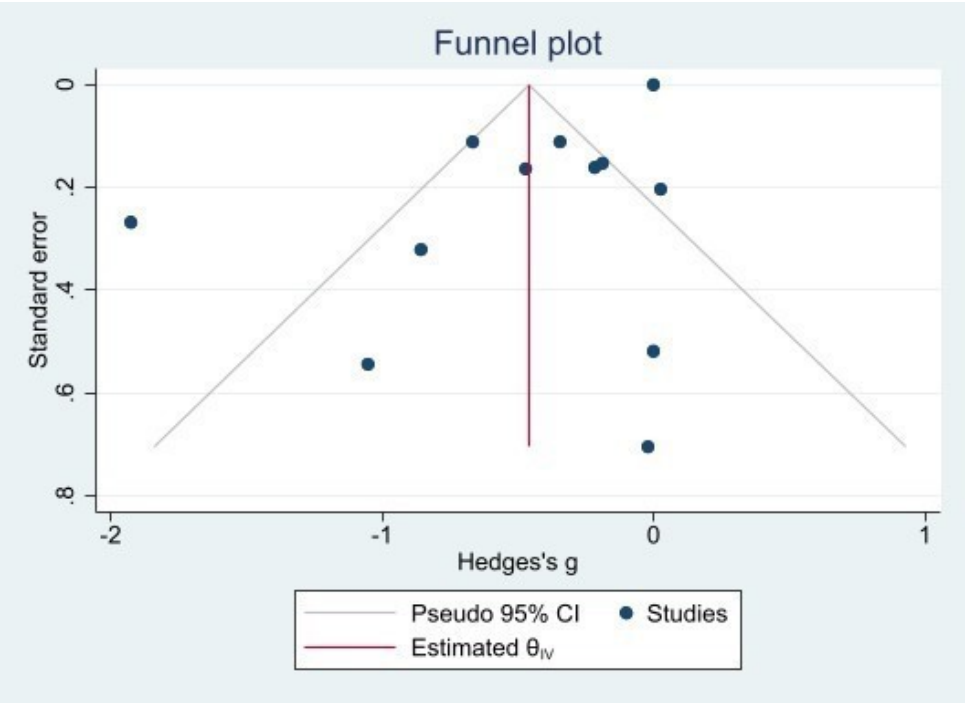


Figure 2—11 Funnel plot for pain

Subgroup analyses: Due to high clinical and statistical heterogeneity sub-group analyses were conducted for pain and physical function outcomes. Eight studies out of twelve had usual care as comparator and were investigated for their overall effect size. Studies that had usual care as a comparator (Figure 2—12) showed statistically significant effects (ES -0.52, 95%CI -0.96, -0.09) but high statistical heterogeneity (I2 = 91.63%). High heterogeneity was detected for physical function (I2=76.70%) with the overall ES for physical function (-0.56, 95%CI -0.84, -0.27).

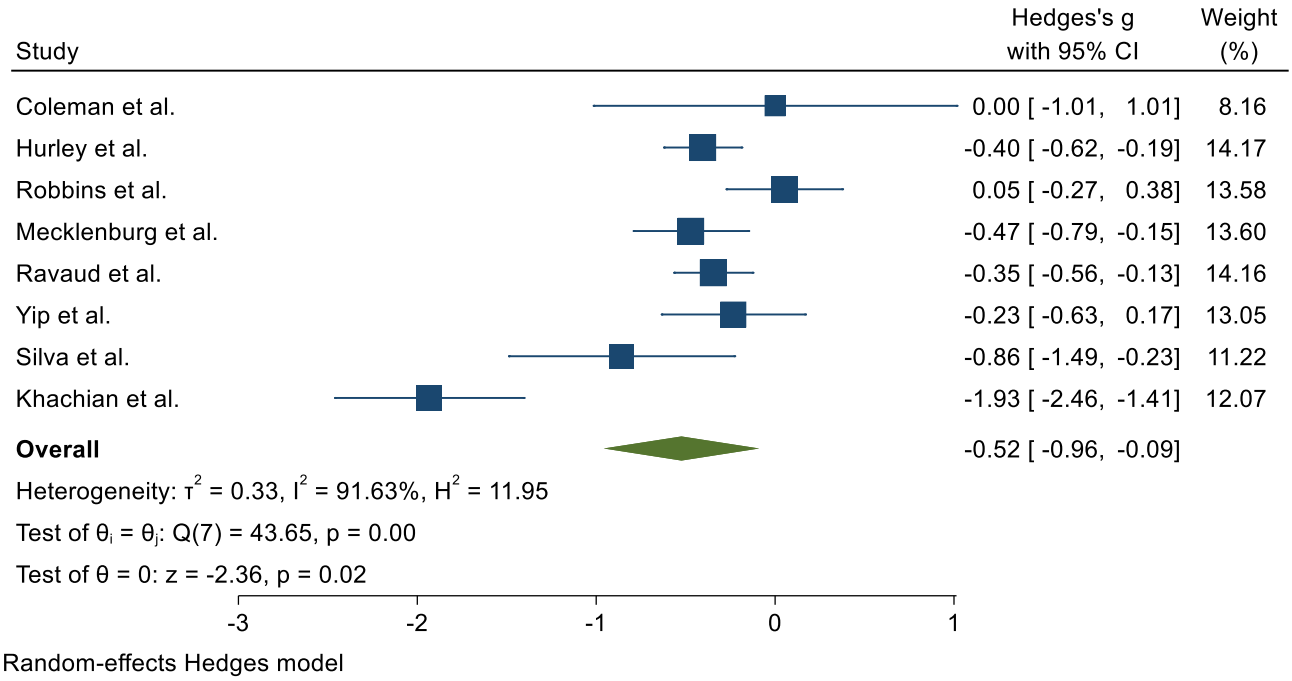


Figure 2—12 Forest plot subgroup analysis comparing complex intervention versus usual care for pain.

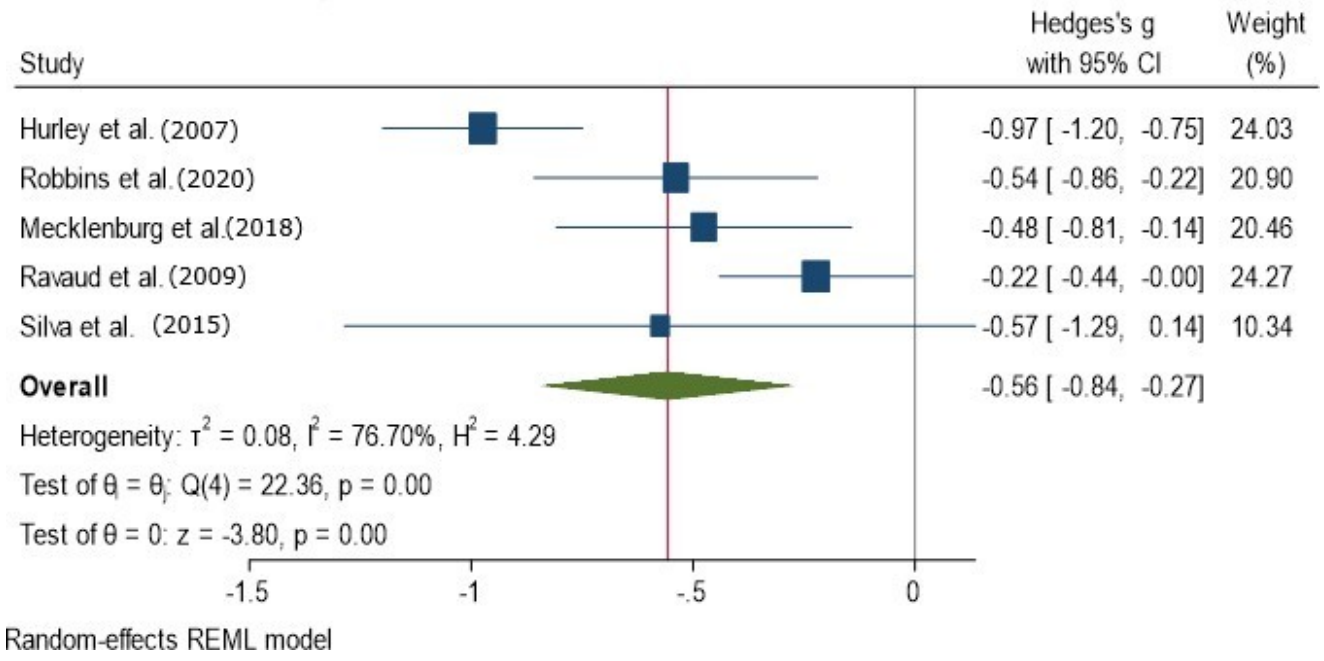


Figure 2—13 Forest plot subgroup analysis comparing complex intervention versus usual care for physical function

Studies with high methodological quality (overall low risk of bias), and sample size (>100 people in both arms), were also examined. Sub-group analyses of high-quality studies for pain and physical function outcomes (*Figure 2—14* & *Figure 2—15*) have shown moderate statistical heterogeneity (I2=59.74% and I2=70.83% respectively), and statistically significant effects (p<0.05) for pain (ES -0.38, 95%CI -0.69, -0.07) and physical function (ES -0.56, 95%CI -0.87, -0.25) outcomes.

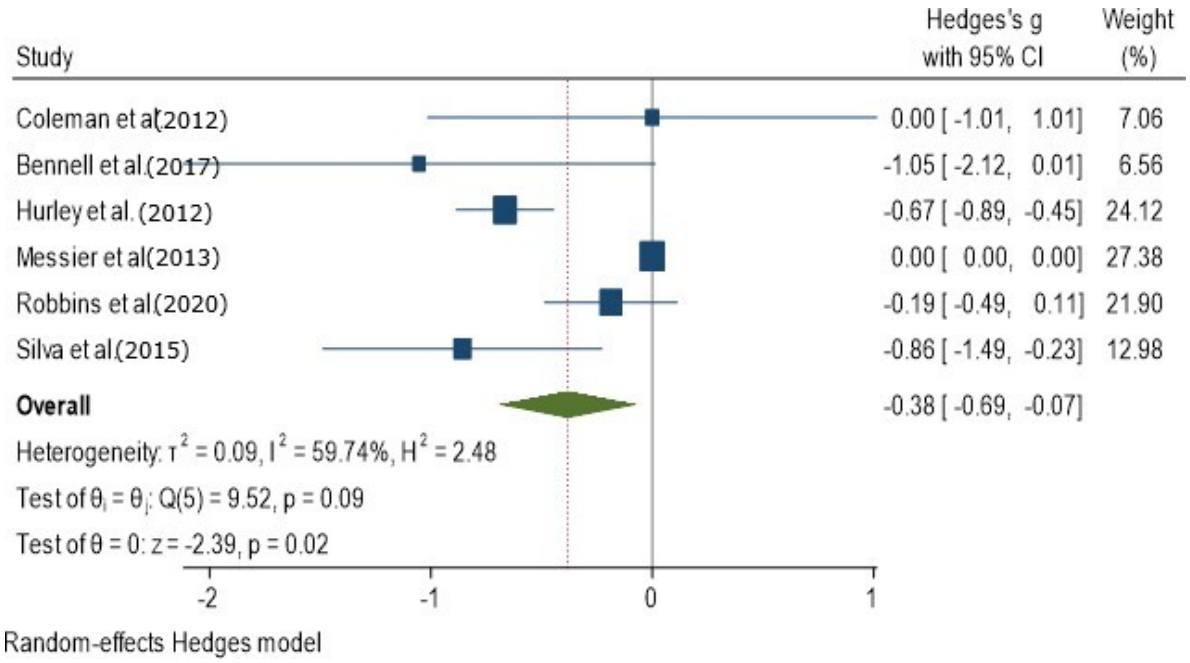


Figure 2—14 Forest plot subgroup analysis of high-quality studies for pain

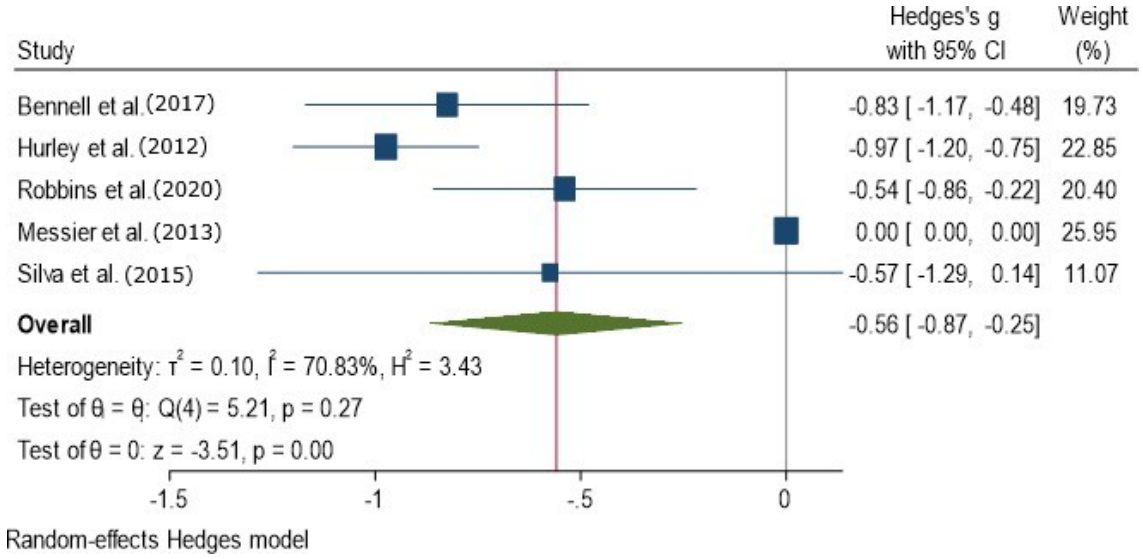


Figure 2—15 Forest plot subgroup analysis of high-quality studies for physical function

Sub-group analyses of studies with more than 100 participants in both arms (Figure 2—16) showed no statistical heterogeneity for pain (I^2=0%) but high statistical heterogeneity (Figure 2—17) for physical function (I^2=83.78%). Statistically significant effects for pain (ES -0.41, 95%CI -0.53, -0.30) and physical function (ES -0.49, 95%CI -0.80, -0.18) were observed for these larger studies.

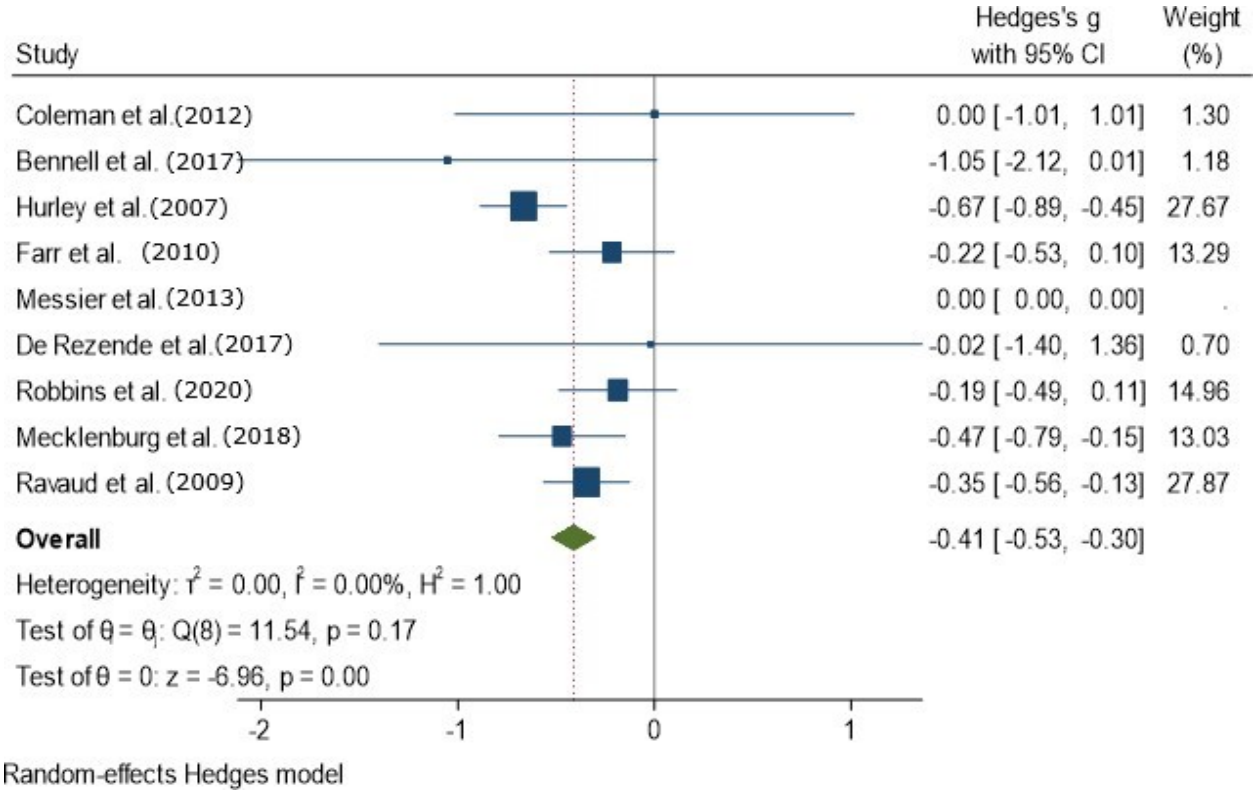


Figure 2—16 Forest plot, subgroup analysis of sample size more than 100 people for pain

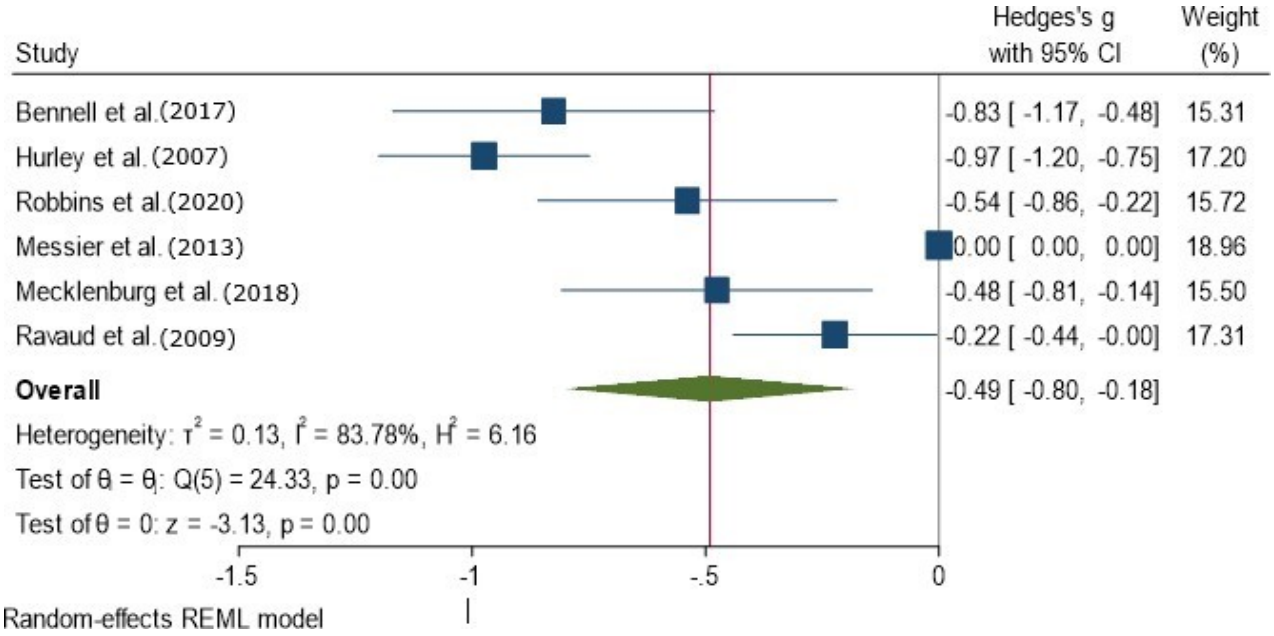


Figure 2—17 Forest plot, subgroup analysis of sample size more than 100 people for physical function

Sub-group analyses were conducted for interventions that were delivered online, face-to-face, on individual and group levels, and still showed benefits for pain and physical function. However, these were few studies and therefore had low statistical power. Figure 2—18 shows that a complex intervention that was delivered online showed benefit for pain but this was not statistically significant (p=0.05), while an online delivered complex intervention showed benefit and statistical significance (P=0.00) for physical function (Figure 2—19).

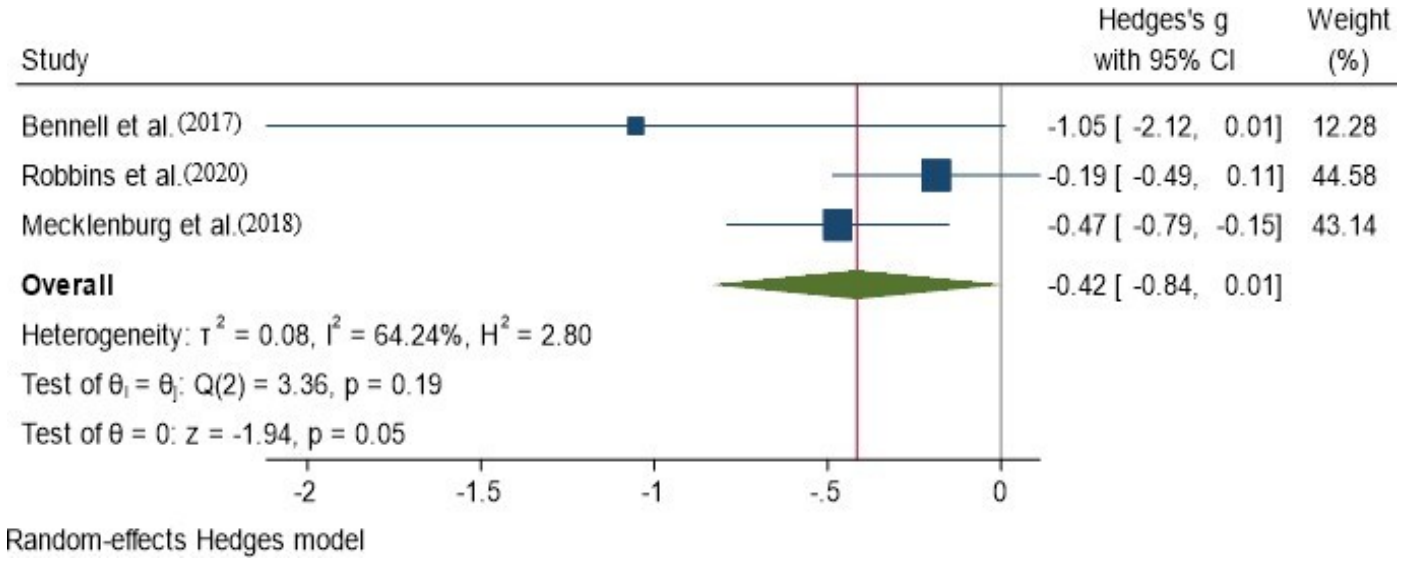


Figure 2—18 Forest plot – Online interventions: Pain

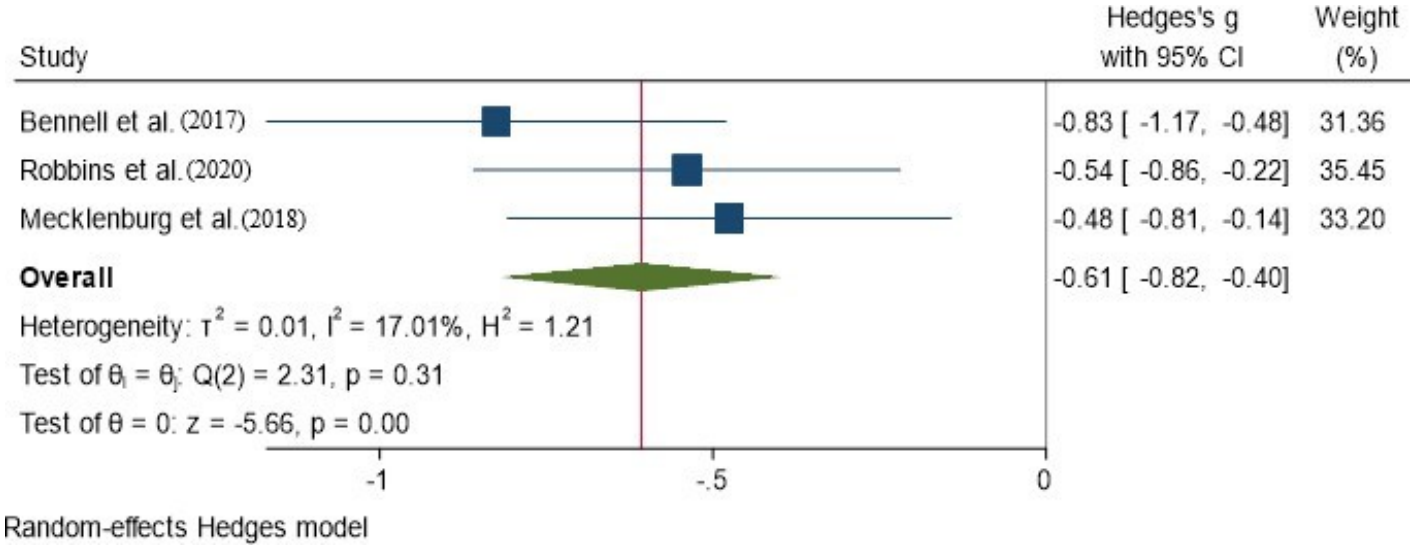


Figure 2—19 Forest plot – Online interventions: Physical function

Complex interventions delivered face-to-face were statistically significant for pain and physical function but both with high heterogeneity (Figure 2—20 & Figure 2—21).

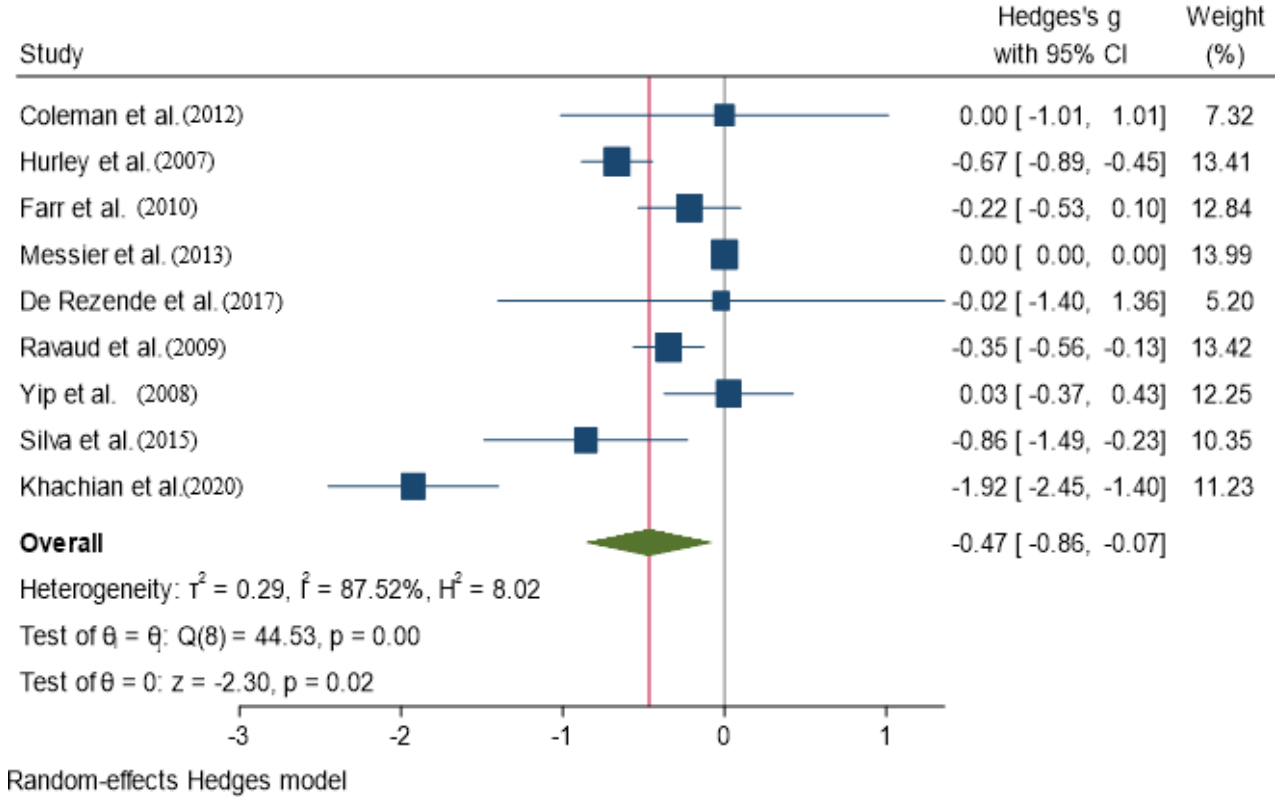


Figure 2—20 Forest plot – face-to-face interventions: pain

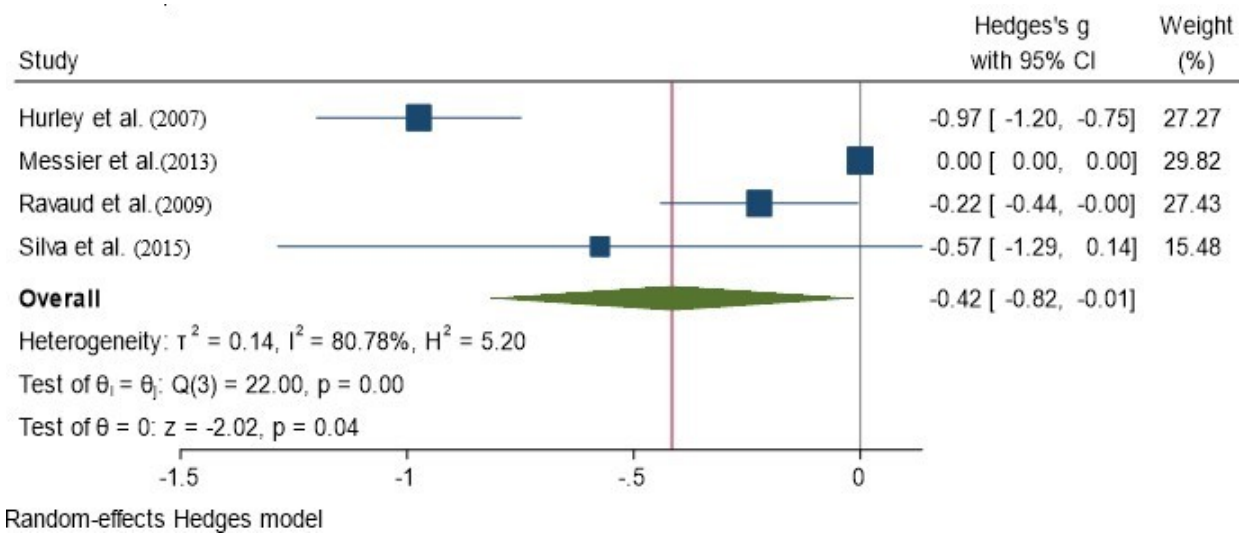


Figure 2—21 Forest plot- face-to-face interventions: physical function

Individual delivered interventions for pain and physical function were statistically significant with moderate and high heterogeneity respectively (Figure 2—22 & Figure 2—23)

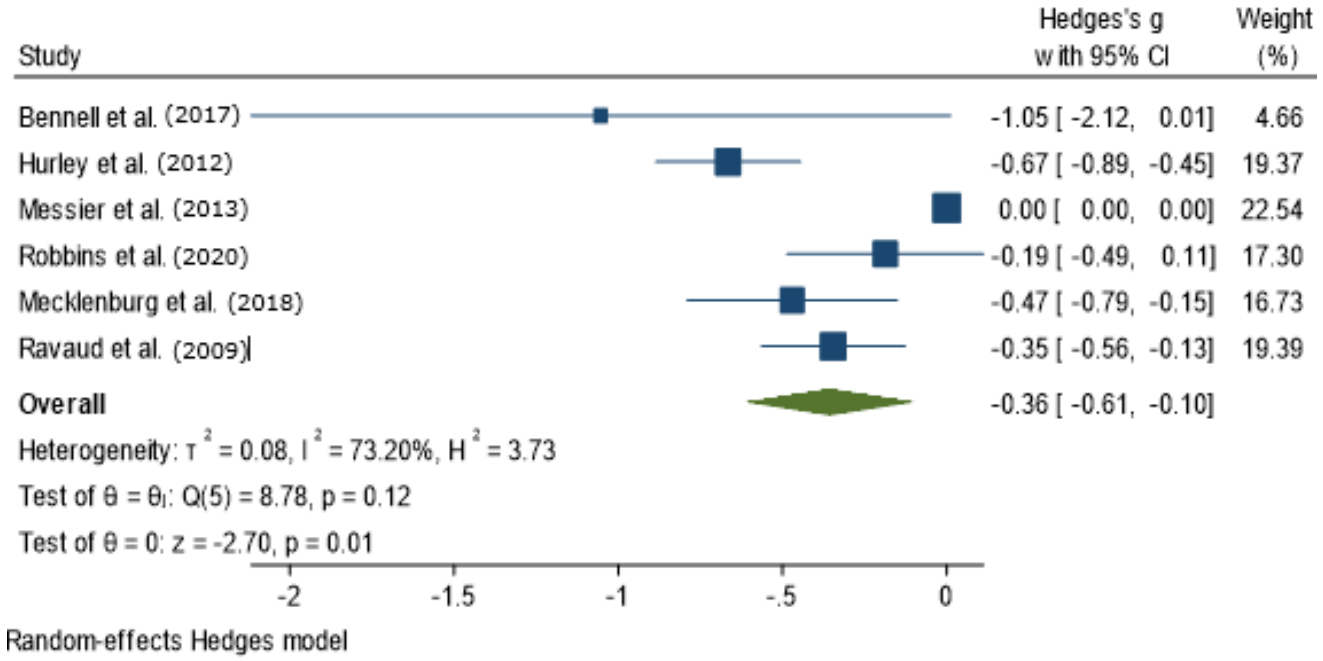


Figure 2—22 Forest plot individual delivered interventions for pain

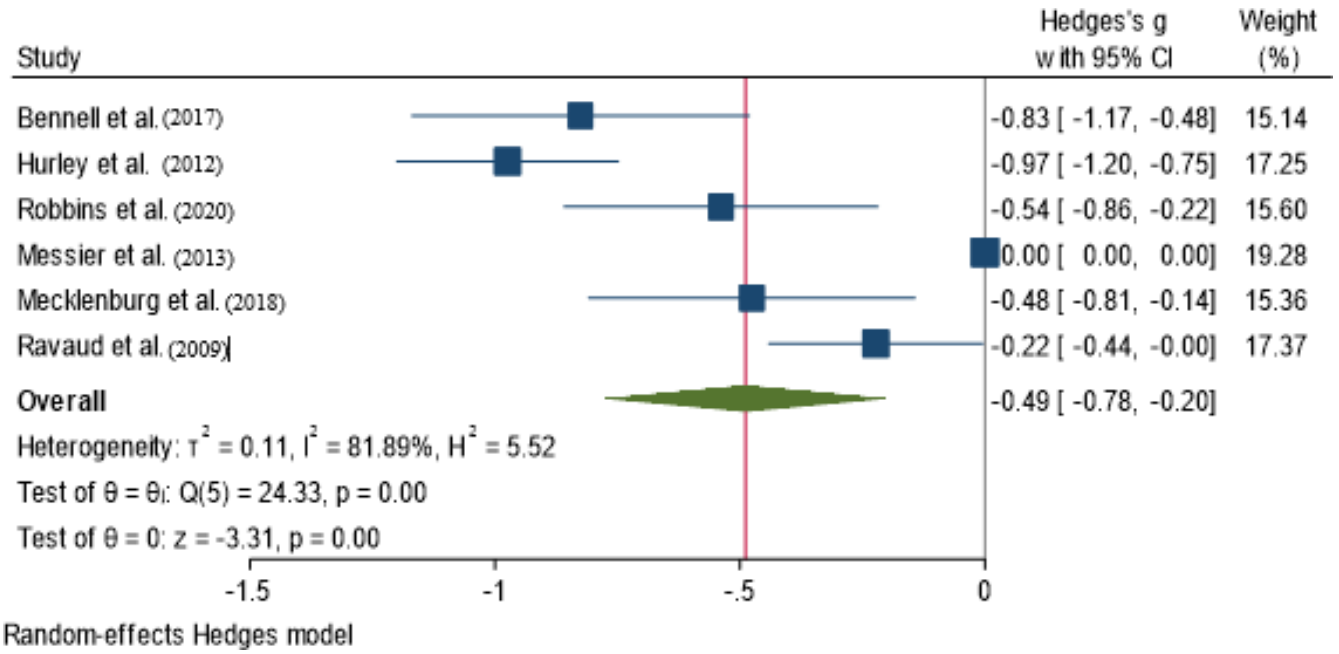


Figure 2—23 Forest plot individual delivered interventions depicting standardised effect sizes for physical function

The group delivered interventions showed significant benefit for pain and function, but this was not statistically significant for physical function (Figure 2—24 & Figure 2—25). High and moderate heterogeneity were found respectively.

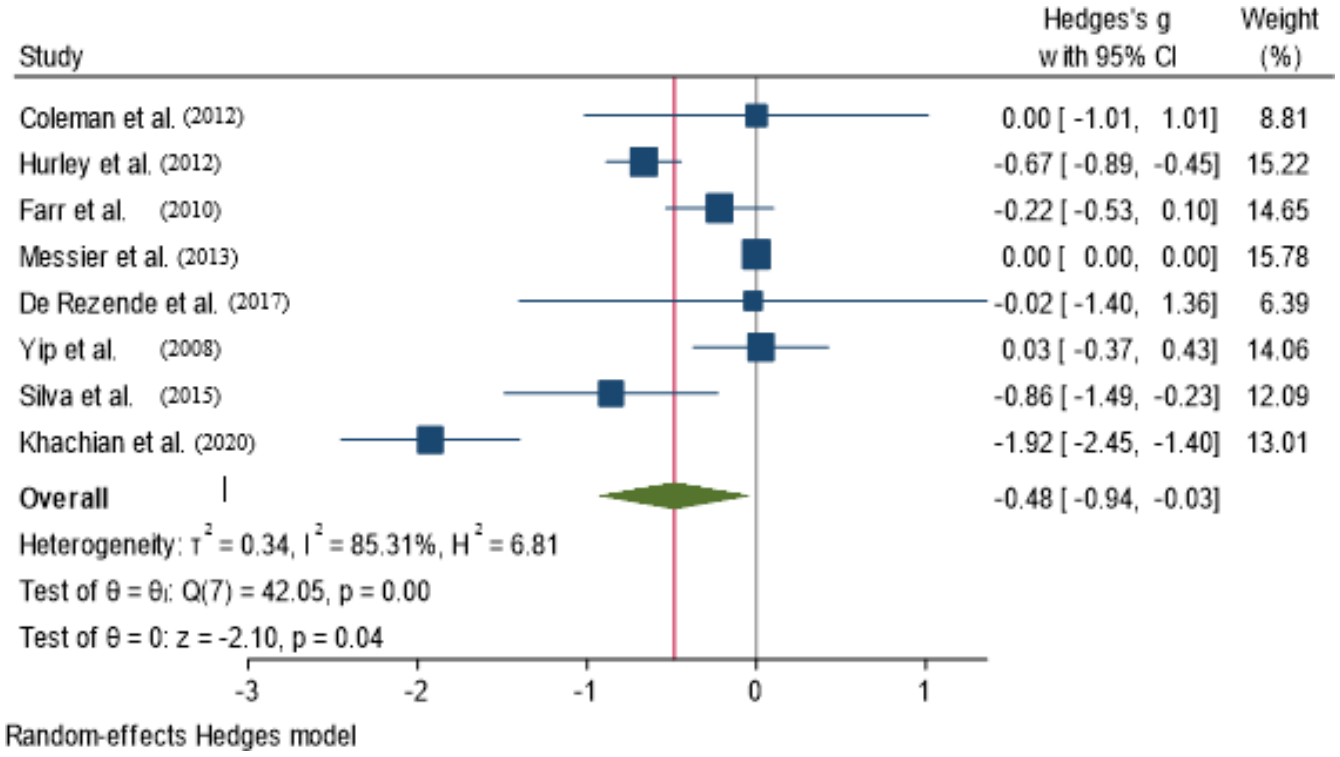


Figure 2—24 Forest plot group delivered interventions for pain

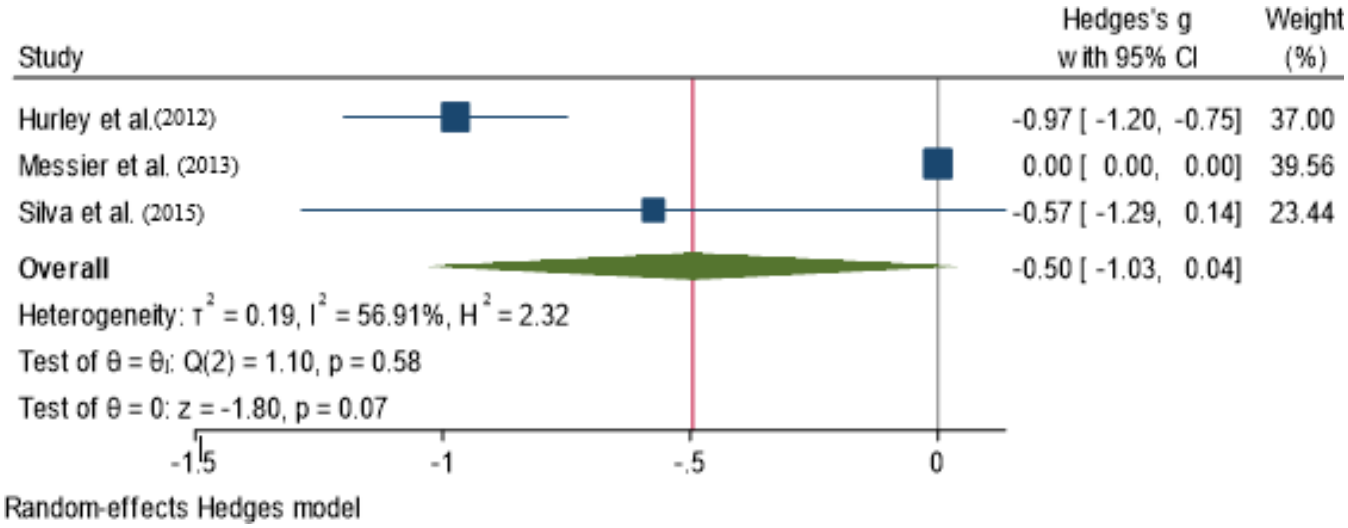


Figure 2—25 Forest plot group delivered interventions for physical function

Subgroup analyses were also conducted for studies that utilised learning theories as part of their interventions, studies that used multidisciplinary approaches, and those that used intra disciplinary approaches. Overall, ES of studies (Figure 2—26 & Figure 2—27) that included learning theories (social cognitive theory, bandura concept, cognitive behaviouraltherapy) as part of their intervention was lower (ES -0.27, 95% CI -0.59, 0.06) for pain compared to those who did not use a learning theory (ES -0.59 -1.07, -0.11) but this was not statistically significant (p=0.11).

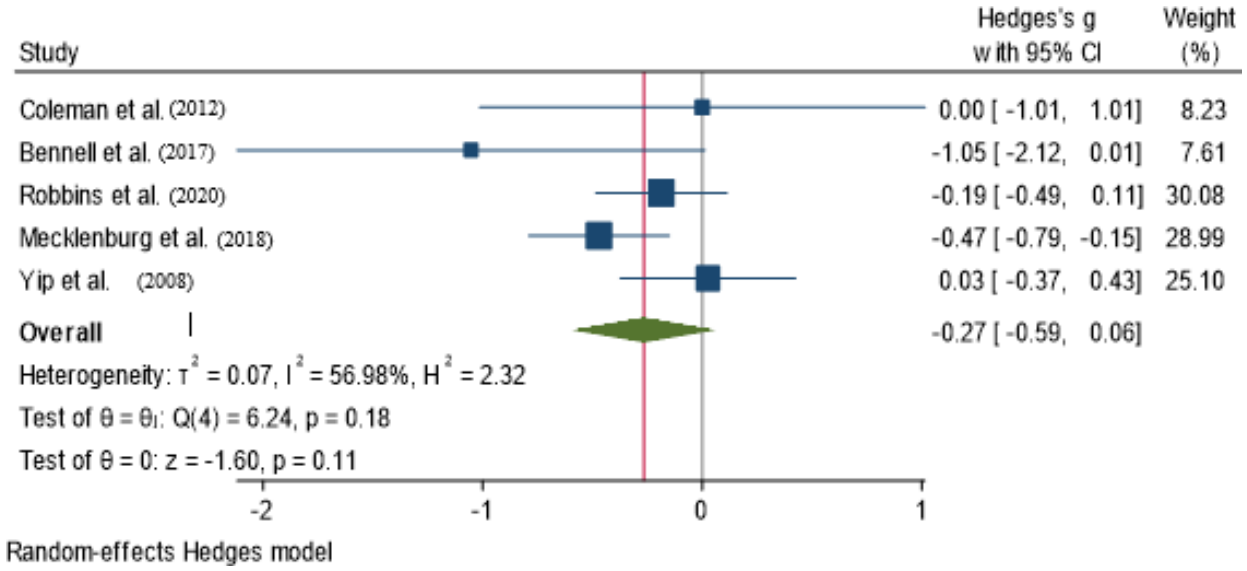


Figure 2—26 Forest plot studies that used learning theories as part of their intervention

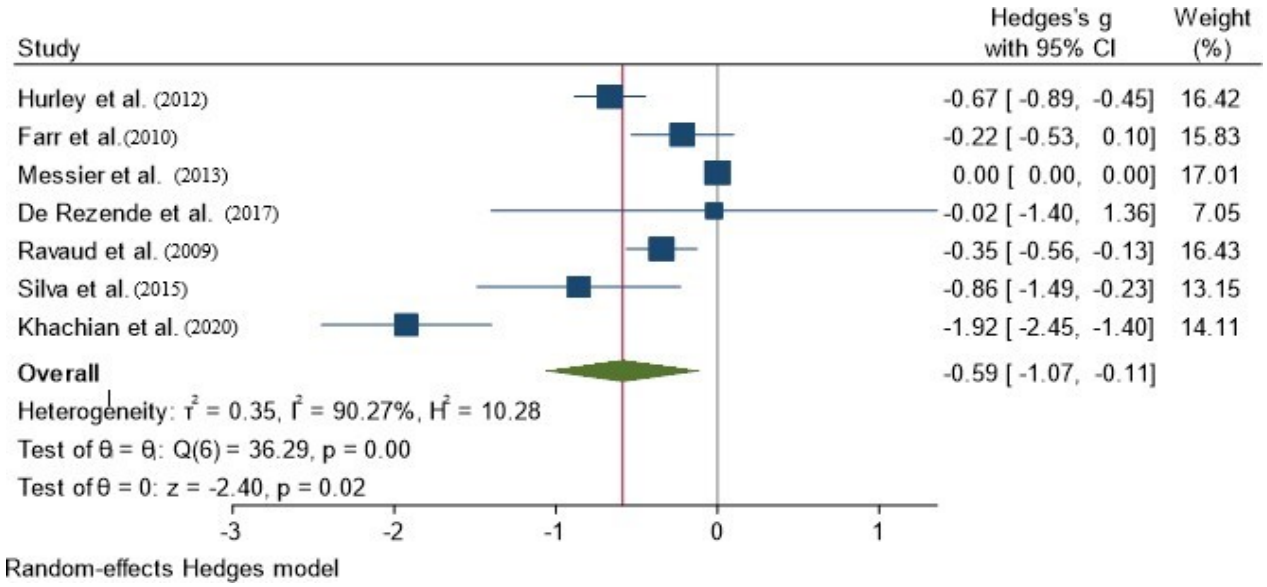


Figure 2—27 Forest plot excluding studies that used learning theories as part of their intervention

On the other hand, studies that used learning theories found a significant benefit for physical function compared to those that did not (Figure 2-44 & Figure 2- 45).

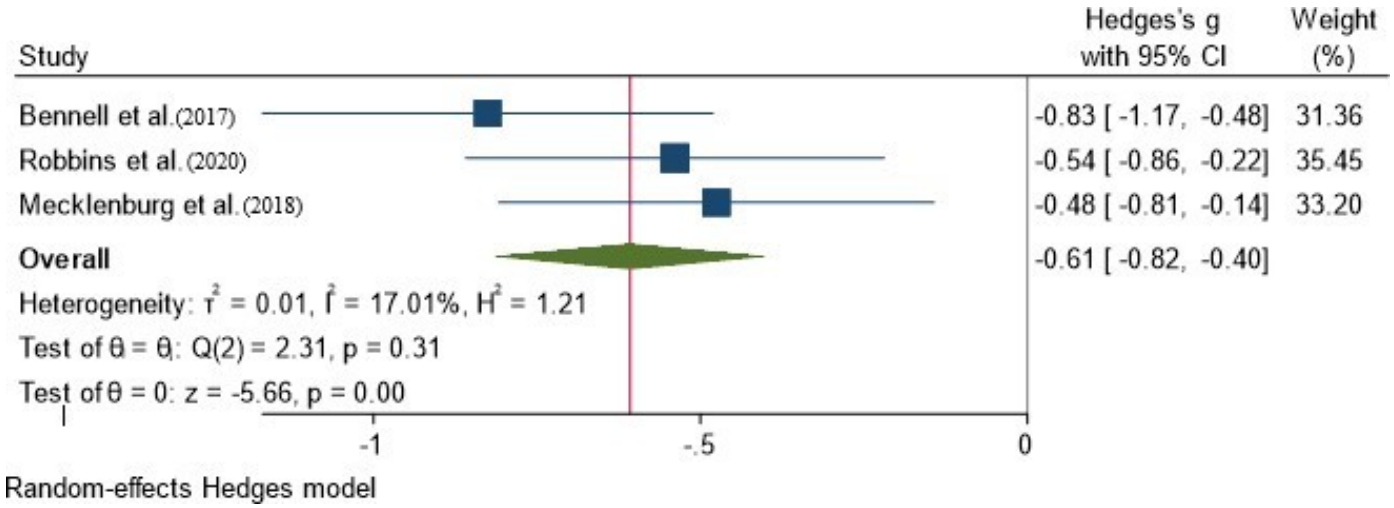


Figure 2—28 Forest plot studies that used learning theories as part of their intervention for physical function

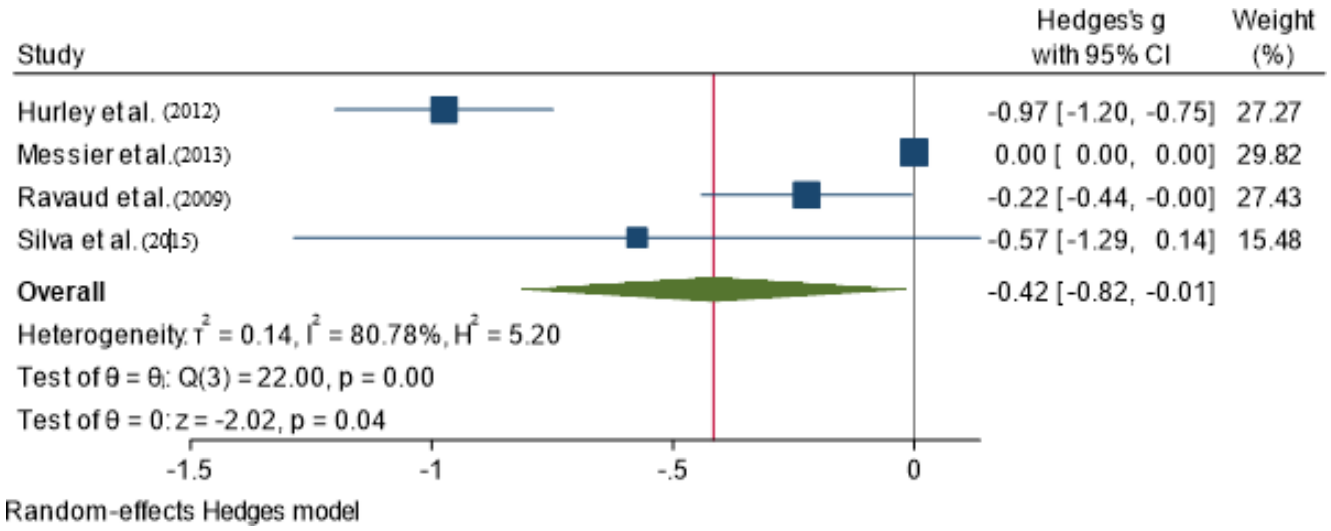


Figure 2—29 Forest plot for physical function excluding studies that used learning theories as part of their intervention

Intra disciplinary approach showed more benefit for pain compared to a multidisciplinary approach (Figure 2—30 & Figure 2—31) but was not statistically significant (p=0.08).

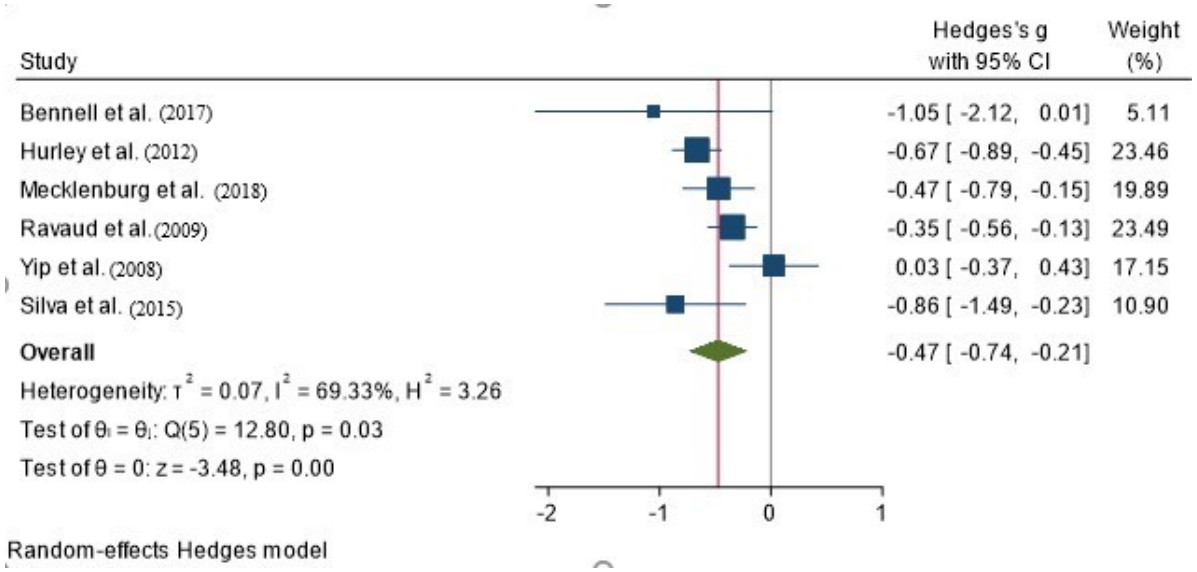


Figure 2—30 Forest plot of intradisciplinary delivered approach for pain

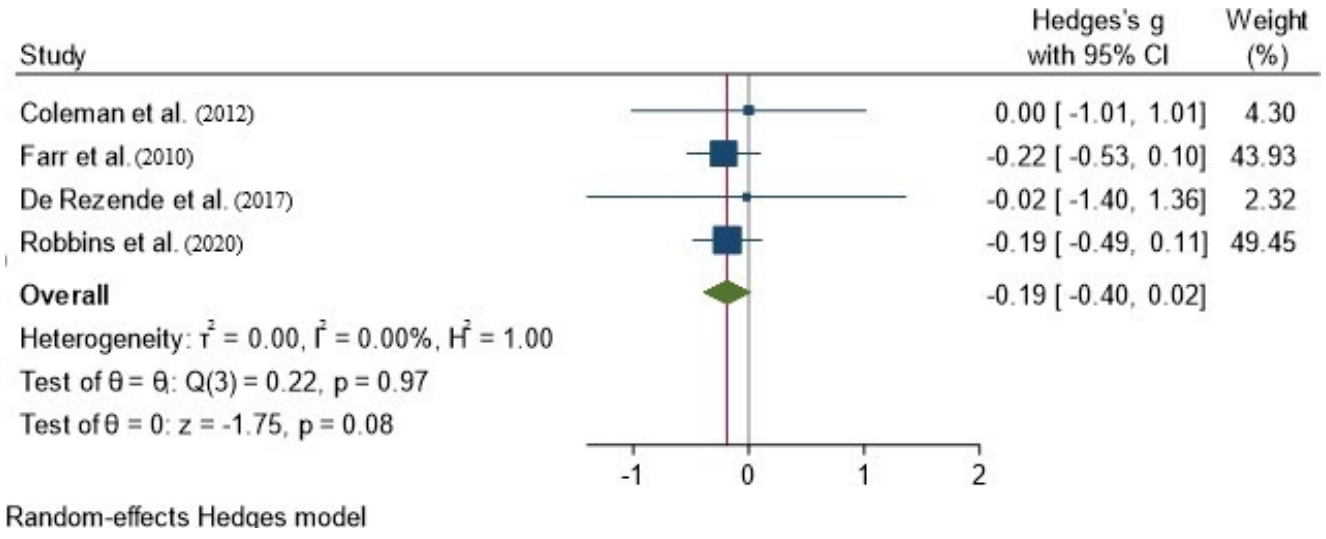


Figure 2—31 Forest plot of multidisciplinary delivered approach for pain

Intra disciplinary approach for physical function has shown statistical benefit (Figure 2—32). There were not many studies to performanalysis for physical function on a multidisciplinary approach.

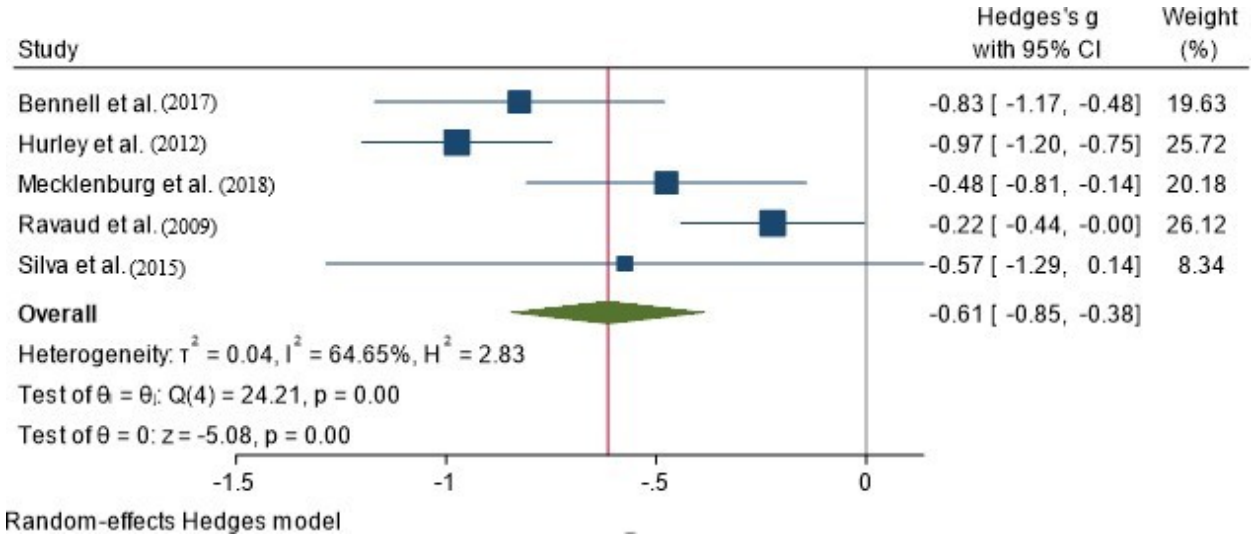


Figure 2—32 Forest plot of intradisciplinary delivered approach for physical function

Physiotherapist delivered intervention (Figure 2—33) has shown statistical benefit for pain (ES -0.62, 95% CI -0.87, -0.36).

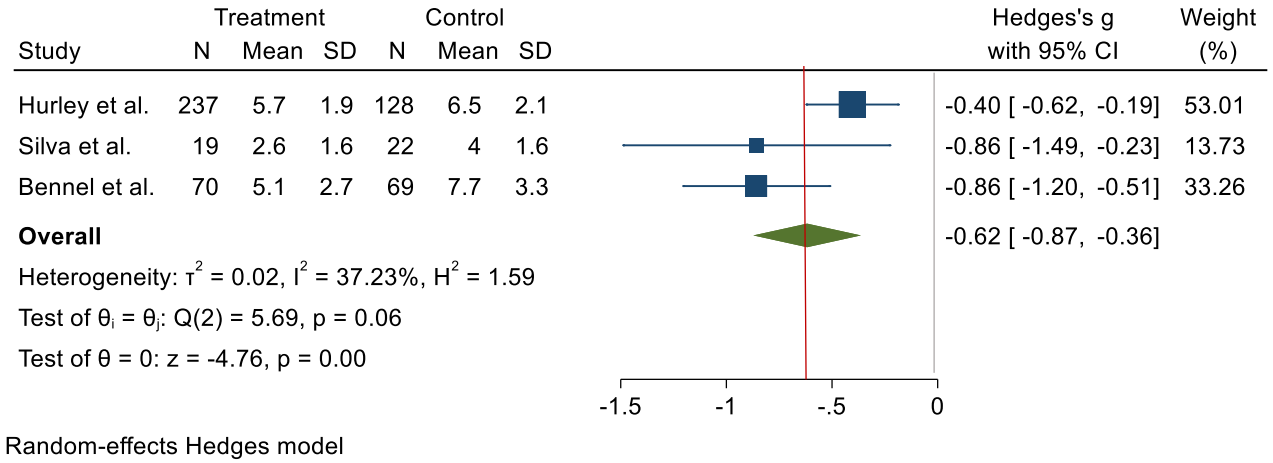


Figure 2—33 Forest plot of physiotherapist delivered intervention for pain.

Physiotherapist delivered intervention has shown statistical benefit for physical function (ES -0.91, 95% CI -1.09, -0.72)

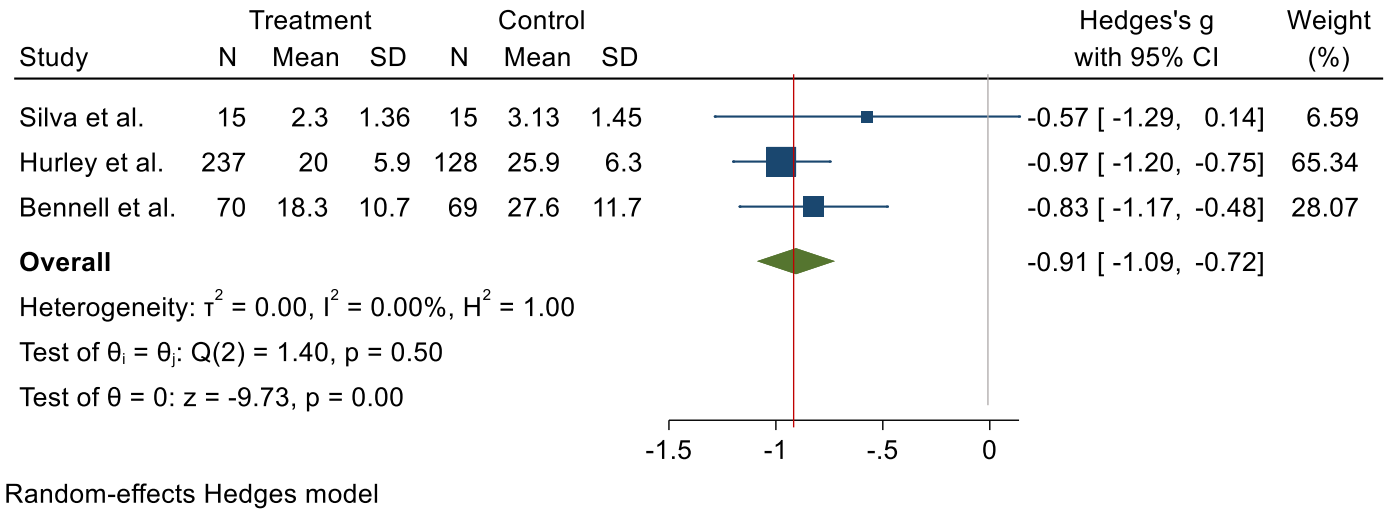


Figure 2—34 Forest plot of physiotherapist delivered intervention for physical function.

Sensitivity analysis: This sensitivity analysis includes the period from the end of the intervention to the primary outcome assessment. The overall effect size for pain (Figure 2—35) was not found statistically significant (p=0.05) when the primary outcome was measured between week one and week 17 (ES -0.74, 95% CI -1.48, 0.00).

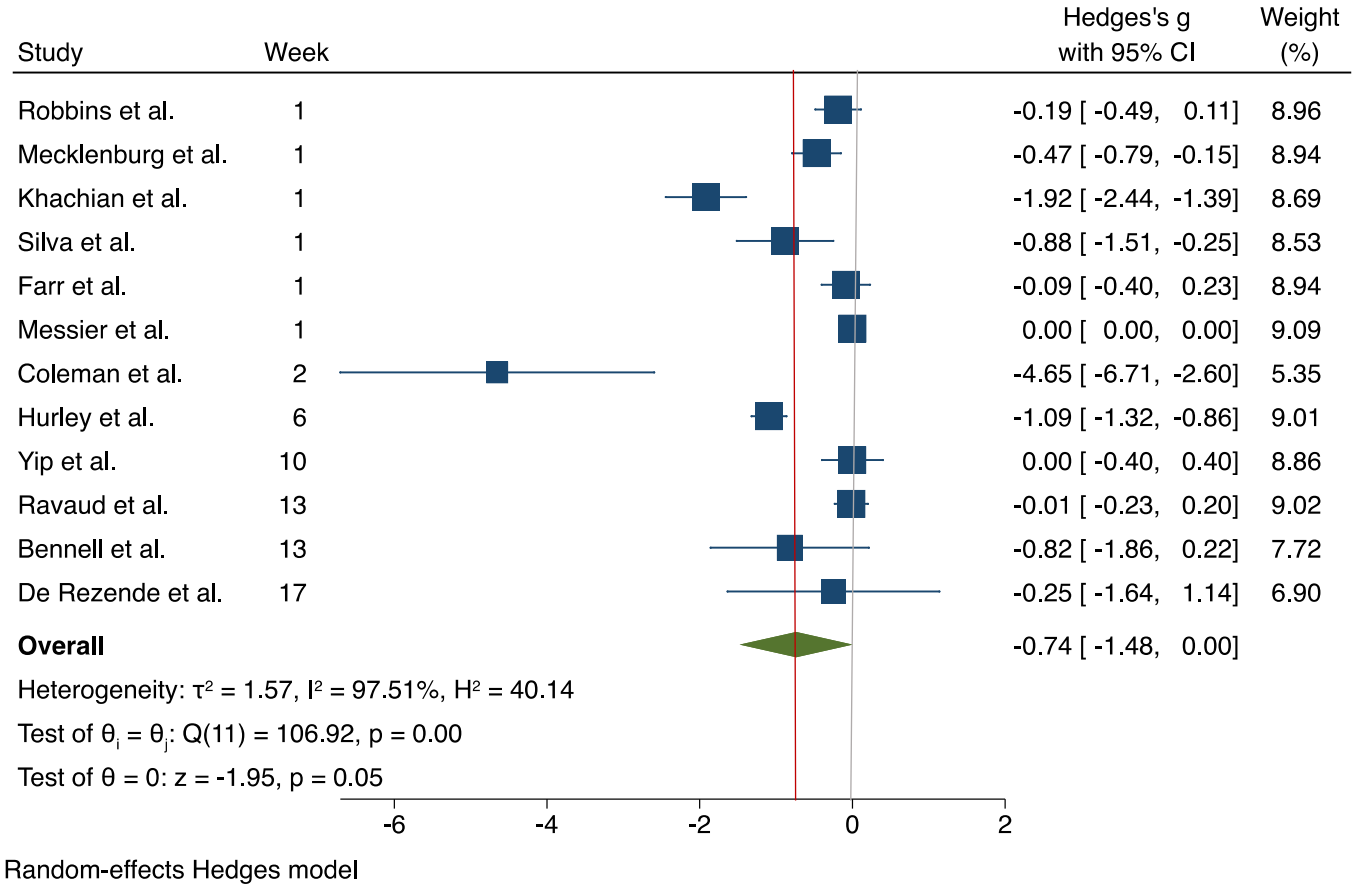


Figure 2—35 Forest plot sensitivity analysis for pain (weeks 1-17)

Funnel plot for pain has indicated the potential for publication bias as outliers and asymmetry were identified (Figure 2—36)

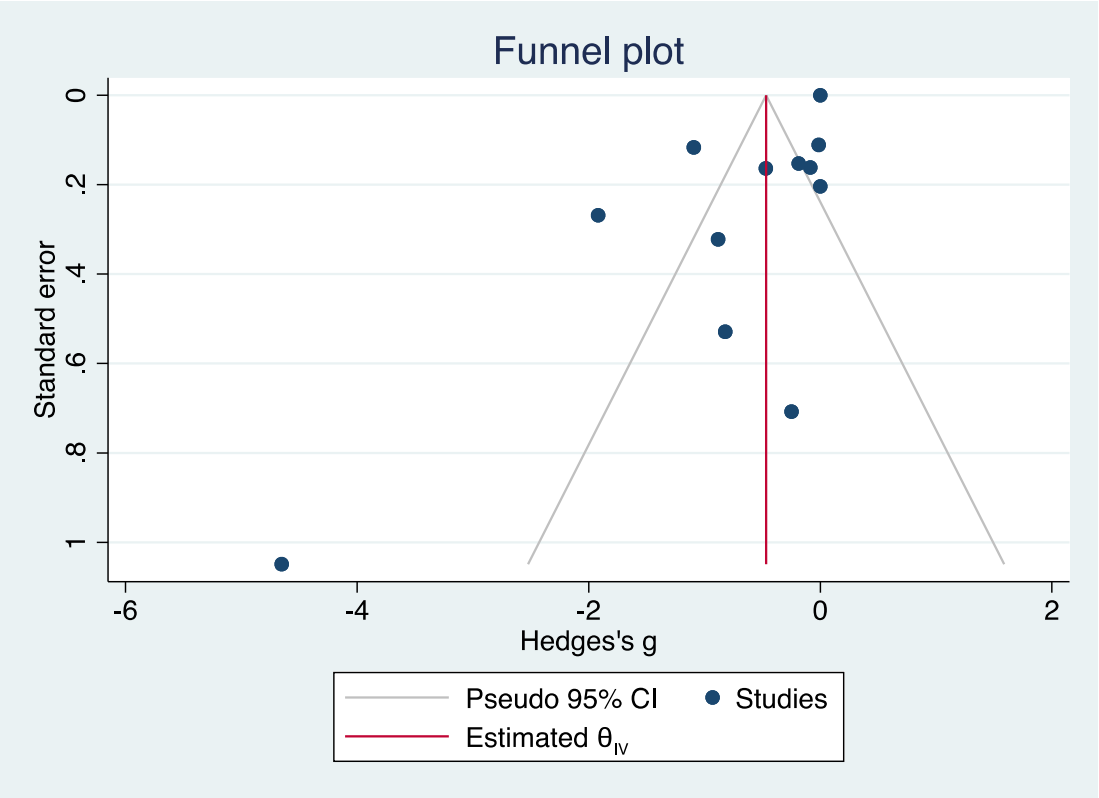


Figure 2—36 Funnel plot sensitivity analysis for pain

The overall effect size for physical function (Figure 2—37) was statistically significant (p=0.01) when the physical function was assessed at weeks 1-13 (ES -0.60, 95% CI -0.79, -0.41)

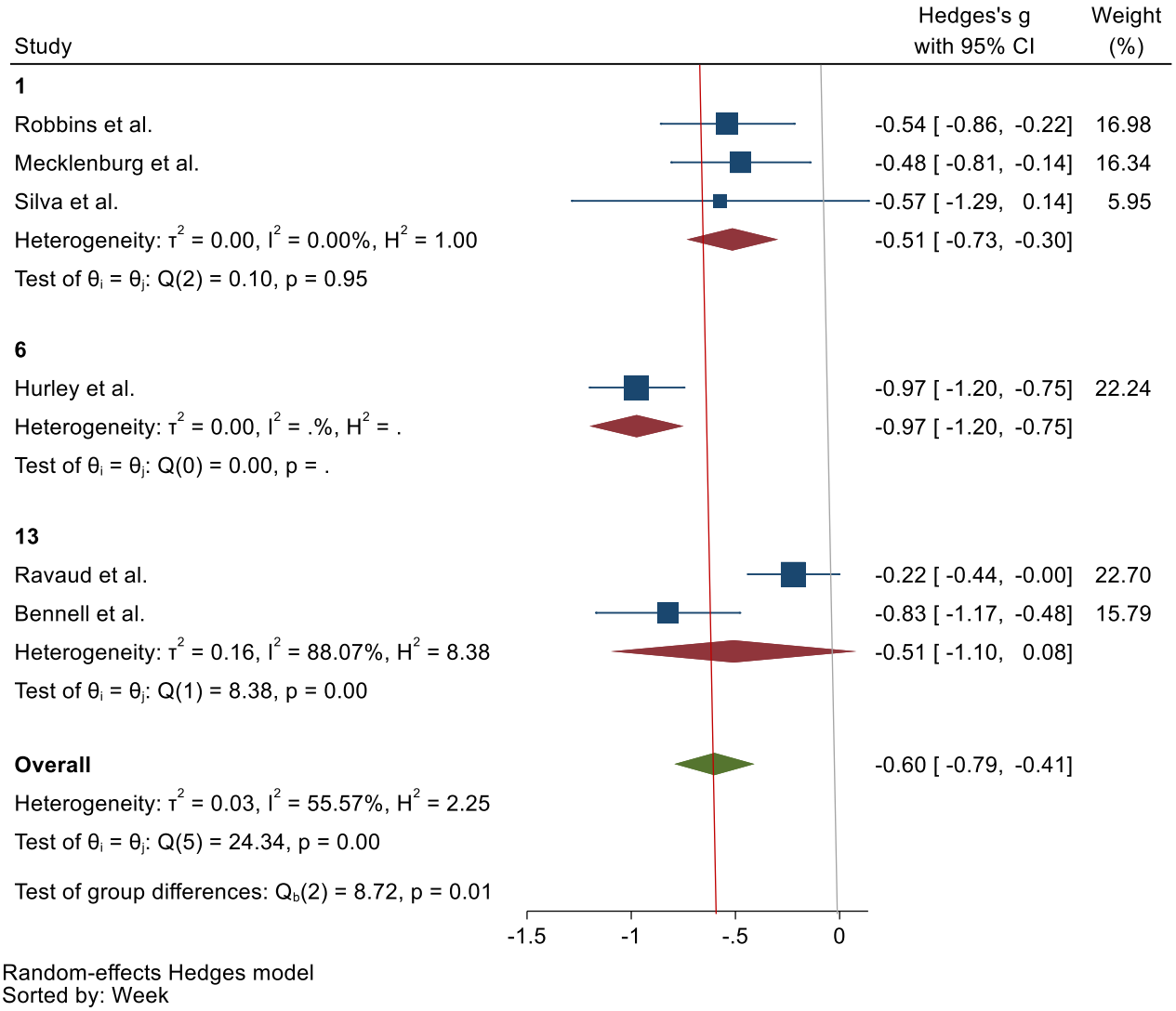


Figure 2—37 Forest plot sensitivity analysis for physical function (Weeks 1-13)

It has been shown that multiple testing increases the type of one error (false positives) (Noble, 2009) and there were multiple studies with marked heterogeneity in this thesis. To correct that, we used a practical and powerful approach to multiple testing as described by Benjamini and Hochberg (1995). The subgroup items that were found non-significant after performing the correction for multiple testing were: face to face interventions for physical function, group delivered interventions for pain, online delivered interventions for pain, group delivered interventions for physical function, multidisciplinary approach for pain, learning theories for pain. Table 2—13 provides the details of the subgroup items that were deemed non-significant after adjusting for multiple testing.

Table 2—13 Adjusted p –values using the Benjamini and Hochberg approach.

Subgroup	p-values	Rank	p -adjusted
Complex intervention versus usual care for physical function	0	1	0
High-quality studies for physical function	0	2	0
Sample size more than 100 people for pain	0	3	0
Sample size more than 100 people for physical function	0	4	0
Online interventions: Physical function	0	5	0
Face-to-face interventions: pain	0	6	0
Individual delivered interventions for physical function	0	7	0
Used learning theories (physical function)	0	8	0
intradisciplinary delivered approach for pain	0	9	0
intradisciplinary delivered approach for physical function	0	10	0
Physiotherapist delivered intervention pain	0	11	0
Physiotherapist delivered intervention physical function	0	12	0
Individual delivered interventions for pain	0.01	13	0.017692308
Complex intervention versus usual care for pain	0.02	14	0.032857143
High-quality studies for pain	0.02	15	0.030666667
Not used learning theories (pain)	0.02	16	0.02875
Face-to-face interventions: physical function	0.04	17	0.054117647
Group delivered interventions for pain	0.04	18	0.051111111
Not used learning theories (physical function)	0.04	19	0.048421053
Online interventions: Pain	0.05	20	0.0575
Group delivered interventions for physical function	0.07	21	0.076666667
multidisciplinary delivered approach for pain	0.08	22	0.083636364
Used learning theories (pain)	0.11	23	0.11

2.4 Discussion

In this systematic review and meta-analysis, we demonstrated that a complex intervention comprising of patient education, exercise, and weight loss advice is more beneficial than usual care, or other control single non-pharmacological intervention for knee OA for pain, function, and QoL. The efficacy of complex intervention over usual care with or without any other single pharmacological/non-pharmacological intervention showed its greatest improvement for pain relief when the clinically important time point was measured at week 13. This was when the study had the appropriate power to detect clinically and statistically significant effects. The results were not statistically significant for pain when the primary outcome was measured immediately after the end of the intervention. The overall efficacy of the intervention on physical function continued to improve over time as physical function maintained its improvement on both occasions: when the clinically important time-point was measured and when the primary time-point was measured immediately after the end of the intervention. These results may explain the differences in nature between those outcomes, and presumably suggest that pain and physical function are outcomes that may be inversely associated to their overall efficacy over time.

A recent systematic review (Goh et al., 2019) also found that the efficacy of exercise intervention tends to peak at 8 weeks and this is similar to our findings. Small short-term improvements in pain due to OA are also reported by previous studies that used aquatic therapy exercises as part of their intervention (Bartels et al., 2016, Waller et al., 2014). With regards to physical function, the most recent and relevant meta-analysis that investigated non-pharmacological interventions for knee OA (RM et al., 2019), also reports a slightly different behaviour of pain compared to physical function outcome. They found statistical significance for WOMAC physical function ($p<0.01$) subsequently at week 4 and not immediately after the end of the intervention (week 3). On the contrary, pain showed its highest improvement at week 3 with no significant statistical differences reported subsequently between groups at week 6 ($p=0.06$) and week 12 ($p=0.32$) respectively. Their

results are similar to our findings and physical function outcomes improved over time. Although, their study (RM et al., 2019), reports the MD of each outcome measure (WOMAC, VAS) rather than the SMD. A previous systematic review (Wang et al., 2012) examined the effectiveness of physical therapy interventions for people with chronic knee pain. They report low strength evidence on the effects of aerobic and strengthening exercise, ultrasound, and Tai Chi. These interventions though, reduced knee pain and improved physical function. However, in their study, they have not compared combined interventions and therefore their results are not generalisable to physiotherapists as physical therapy is administrated as a combined intervention. Similarly, White et al. (2007) evaluated the effects of acupuncture for people with chronic knee pain in a systematic review and meta-analysis. They reported that acupuncture is superior to sham acupuncture and to no additional treatment in pain and physical function. They found moderate benefit for pain relief ES (0.4, 95% CI 0.1, 0.6) which is similar to ours.

Quality of life was measured using a variety of generic and specific outcome measures andonly two studies were included in the meta-analysis to assess their efficacy (Hurley and Walsh, 2012, Khachian et al., 2020). The outcome measures used were the 36-Item ShortForm Survey (SF-36), 12-item Short Form Survey (SF-12), quality indicators, Assessmentof Quality of Life II instrument (AQoL-2), McMaster Toronto Arthritis patient preference questionnaire (MACTAR), Knee Injury and Osteoarthritis Outcome Score (KOOS), and theEuropean Quality of Life Five Dimension (EQ-5D-5L). Although most studies reported the SF-36 as generic health-related quality of life measure, it has been criticised by its' developers, for not providing a global measure of health-related quality of life and a totaloverall score was not possible to be obtained from the questionnaire (Lins and Carvalho, 2016). Despite this, many studies (75%) use it without specifying the method for calculating the SF-36 total score. For this reason, we were unable to include the studies that used the SF-36 in our meta-analysis. Quality of life measured by KOOS subscale and MACTAR was significantly improved for the intervention group compared to control. Not many studies reported outcome data related to anxiety/depression and therefore it was not possible to quantify those.

RCTs, in which their allocated treatment is not concealed, and therapists, and participantsare not blinded to the assigned treatment tend to report larger effect sizes than higher- quality trials with adequate blinding and concealed treatment allocation (Schulz et al., 1995). In our study, a great proportion of RCTs showed the high risk of bias in domains such as allocation concealment and blinding of outcome assessors in addition to inadequate blinding of participants and investigators that was due to the nature of the intervention. We preferred to use the Cochrane RoB tool compared to the Physiotherapy Evidence Database (PEDro) scale as the latter provides a summary quality score and is not encouraged to be used for quality assessment in trials (da Costa et al., 2013). Moreover, substantial disagreement was found between those two methods (RoB, PEDro)in items such as generation of random sequence, concealment of allocation, and blinding of outcome assessors in previous reviews (Armijo-Olivo et al., 2015).

We found that completeness of intervention reporting was poor with reporting being worse for the control interventions. Overall, only three trials (Farr et al., 2010, Kawi et al., 2015, Palmer et al., 2010) were well reported. Completeness of intervention reporting was assessed using the TIDieR checklist, and summary scores for every item across all trials show that the most frequent items the trials adequately reported were "Intervention name" (item 1) and "what was done" (item 4). Most frequently items poorly reported were"how well was the intervention delivered" (item 9), and if the intervention was tailored or modified (item 12). In our systematic review, most studies described the control intervention as "usual care" or "standard medical management" and that might have obscured the accurate interpretation of the effect size of the intervention, as well as hampered synthesis and comparisons in other systematic reviews and clinical practice guidelines (Yamato et al., 2016). This is because control interventions may vary depending on multiple factors such as country, service, and care provider. A previous study has also found poor completeness of descriptions of physiotherapy interventions in a random sample of 200 RCTs investigating gerontology (24%), musculoskeletal (20%), andcontinence and women's health conditions (Yamato et al.,

2016). The findings of our study are consistent with previous studies reporting suboptimal quality of intervention reporting for a variety of surgical and non-surgical interventions (Duff et al., 2010, Jacquier et al., 2006).

Substantial heterogeneity (>70%) in studies that assessed pain and physical function implied that the true underlying effects might be significantly different across studies. The robustness of the results was assessed through numerous subgroup analyses and potential modifiers of efficacy for pain and physical function according to study and methodological characteristics were identified. RCTs with a higher risk of bias slightly inflated the estimation of the overall effect size for pain outcome. The sample size was not a significant determinant of efficacy though, as the effect size of pain did not change significantly ES (-0.41, 95% CI -0.53, -030). However, the CIs greatly narrowed indicating more precision in the overall estimate of the ES for pain. Similarly, studies that included usual care as a comparator did not influence the effect size of pain or physical function.

This suggests that the pooled results obtained were robust and the wide variability between the studies did not have an impact on the results. Online delivered interventions for pain outcome, face to face interventions for physical function, group delivered interventions for pain and physical function may comprise potential determinants of efficacy as these were not statistically significant after correcting for multiple testing. Moreover, studies that used learning theories such as CBT as an add-on, and studies that used a multidisciplinary approach to deliver their interventions, improved the ES for pain but did not show statistical significance. However, a smaller number of studies was included for analysis compared with the analysis for the intra-disciplinary approach, which might have biased the results. Therefore, either there is no effect or the data are inconclusive.

To our best knowledge, this is the first systematic review to assess implementation fidelity strategies (treatment delivery and treatment receipt) in complex RCTs for knee pain due to OA. By reviewing and rating 17 published RCTs that involved 3,069 patients we have shown

that implementation fidelity in healthcare complex interventions for knee pain is under-recognised and poorly reported with only 17.6% of the items with regards to treatment delivery being reported sufficiently while 33.3% are reported sufficiently for treatment receipt. A previous systematic review identified these strategies and also highlighted poor fidelity reporting in palliative care (Ang et al., 2018).

There are strengths and weaknesses in our study. First and foremost, our study provides novelty as this is the first meta-analysis to investigate the efficacy of a complex package of patient education, exercise, and weight loss advice for knee pain due to OA. Rigorous methodological approaches were used to validate our findings. The independent reviewers validated all the extracted data and agreement between the independent reviewers for thetitle and abstract screening was high. The robustness of the results of the meta-analysis was assessed through various subgroup analyses. We have also used Benajmini and Hochberg multiple testing approach to identify the false positives and provided that alongside with the adjusted p-values.

A previous study (Sun et al., 2014), highlighted the criteria for deciding on the credibility of a sub-group analysis. They presented the factors for clinicians and authors to decide ifthe apparent differences in subgroup response are real. These are 1) whether can chancefactor explain the subgroup difference, 2) if the subgroup difference is consistent across the studies, 3) if there is a strong pre-existing biological rationale supporting the subgroupeffect. We showed that our results are credible and reliable as the subgroup differences were consistent across the studies and we provided external evidence of previous studies supporting the subgroup effect. Moreover, the chance factor did not influence our sub- group results as we showed significance for most of them. To correct for type one error, multiple testing error was performed, that was the Benjamini and Hochberg approach which reduced the likelihood of having false positives.

Another strength is that we used the SMD over the MD as our outcomes measured the same

domain using different scales, and the SMD standardises outcomes before pooling them in a meta-analysis (Murad et al., 2019). Some of the included studies had small sample sizes that might lead to a biased overestimation of the SMD (Borenstein et al., 2021). Hedges' was used in this study to correct the error for small sample sizes (Hedgesand Olkin, 2014). Finally, we contacted all authors for information not reported about patient education and obtained two responses.

A limitation of the study was the small number of studies that were included in the final synthesis. Moreover, we only included trials that were published in English, so our findings may not be generalizable to studies in other languages. In addition, we did not have specific criteria to assess individualisation of intervention as it was judged on whether thepaper clearly stated or if the healthcare professionals negotiated personal goals with the participants.

In conclusion, this meta-analysis showed significant moderate benefits from a complex package of care for pain and physical function outcomes in people with knee OA. The results confirmed the general problem of poor reporting of interventions in trials. The future meta-analysis should consider expanding on the electronic database searching andincluding articles not published in English. They should also consider providing criteria for intervention individualisation and report individualisation degree in detail.

Alongside with the poor completeness of intervention reporting, a key finding of this systematic review is how poorly interventions are reported and how rarely fidelity assessments are done and reported. Therefore, this thesis will provide an original fidelity assessment plan by conducting robust evaluation of fidelity and acceptability (treatment receipt and treatment enactment) and consider its implications for the intervention.

3. Chapter - Methods for developing the intervention

To ensure that nurses have the skills and can deliver the package in the feasibility RCT, we piloted the non-pharmacological intervention with 15-20 participants in the package development phase. The components of the non-pharmacological package have been developed inductively and are recognised and expressed as actions and behaviours from the interaction between the participant and nurse. The inductive process resulted in the generation of an initial fidelity protocol, which was developed through consensus with the health research team. Participants received the non-pharmacological package of care by the nurse comprising education, advice, exercises (aerobic, strengthening, and stretching)and other adjunctive advice in four visits over 5 weeks. Participants were required to attend Nottingham City Hospital and the nurse delivered the treatment in a clinic room. All the consultations were video recorded to assess whether the nurse can deliver the non-pharmacological intervention as intended (fidelity of delivery). Before video recording, nurses and participants were required to provide written informed consent. Face to face, interviews were conducted with participants and nurses after the final study visit. A portable recording device was used to audio record the interviews. The purpose of this was to assess the acceptability of the non-pharmacological intervention and resolve any possible challenges to deliver the non-pharmacological package in a feasibility RCT.

3.1 **Training of the providers (nurse)**

The research nurse delivering the intervention did not have prior practice experience in rheumatology or allied specialties such as orthopaedics, rehabilitation, or sports medicine.This further necessitated training in delivering treatments for arthritis and musculoskeletal diseases. The programme to train nurses to deliver the NICE guidelines was developed by MH and AA. The training was delivered by an academic physiotherapist (MH) and rheumatologist (AA) and focused on the assessment and management of OA following NICE guidelines, exercise prescription (aerobic and strengthening), information and advice to support weight loss, and use of behavioural strategies to motivate patients and enhance adherence. Teaching sessions were delivered in face-to-face sessions and supported by a training manual, case studies, and patient simulation sessions. The training manual outlines the content that will be covered in the teaching sessions which is summarised in Table 3—1. Practical sessions on assessing the participant, delivering and modifying exercise, weight loss advice, and use of strategies to encourage adherence were also included. The exercise menu comprising strengthening and stretching exercises and the Versus Arthritis Research UK booklet (ARUK) for knee OA were e-mailed to the nurses.

Table 3—1 Content of the training manual

Overview of knee OA • What is OA? • What causes OA? • How is it diagnosed? • Signs & Symptoms • How does knee OA progress? • The impact of knee OA on the individual and society
Non-pharmacological management of OA • Core treatments for OA • Adjunct treatments • Patient Advice and information • Weight loss • Exercise • Use of hot/cold/TENS • Walking Aids and Footwear • Pacing • Follow-up and review
Pharmacological management of Osteoarthritis • First-line treatments • Second-line treatment Recommended Analgesic ladder

Principles of exercise

- Physical activity
- Exercise
- Aerobic activity
- Strengthening exercise
- Stretching exercise
- Balance and Co-ordination

Exercises and equipment

Prescribing exercise

- Who can and cannot start exercising safely?
- Taking an exercise history
- The F.I.T.T principles for exercise prescription
- Getting started
- Aerobic activity
- Muscle strengthening
- Progressing exercise

Managing "flares"

Practical sessions

- Practical session: Clinical Examination of the OA knee
- History
- Physical examination:
- Look
- Feel
- Move the joint

Assess the Function of the joint, observe the patient

Practical sessions: Exercises for knee OA

Motivation & Behavioural support strategies for adherence

- Establishing participant preferences
- Setting SMART goals
- Establishing self-efficacy (confidence levels)

Action planning & Exercise diaries

3.2 **Recruitment**

Community-dwelling people with knee pain were recruited. Recruitment occurred from three sources:

Responders from the Investigating Musculoskeletal Health and Wellbeing cohort study (Millar et al., 2020) that self-report knee pain as the predominant joint pain were sent a baseline questionnaire pack enquiring about knee pain and quality of life (WOMAC, HADS, SF-36, EQ-5D-5L). Participants were be asked for willingness to participate in future trials, receive further questionnaires on knee pain, and for their data to be used in comparisons with other participant groups in research studies. Those willing and meeting the eligibility criteria were then be invited to take part in the development phase of the study or randomise into the feasibility cohort RCT.

Participants identified from the screening of GP records for previous consultations of knee pain were sent the knee pain questionnaire pack.

People who have participated in previous research on knee pain and OA conducted by the University of Nottingham, Academic Rheumatology and expressed a willingness to participate in future studies were approached with the knee pain questionnaire back. Participants were recruited from the pool of patients for the overall study.

3.3 **Setting the scene**

Data collection occurred at the Clinical Sciences Building, Nottingham City Hospital in the department of Academic Rheumatology. The camera was pre-positioned using a tripod as shown in Figure 3—1. The camera captured the interaction between the participant and the nurse, and the treatment couch and conversation table were visible on the screen. Thechairs were positioned as indicated in the photograph below. The camera was tested before each visit of the patient to make sure it is working properly. PAN activated the video camera and ensured to reduce the time they look through it to minimise intrusiveness.

PAN set up the equipment to video record the exercise training, giving advice, interview,

discussion, or conversation. Although video recording has not been confirmed to be detrimental to healthcare delivery, participants met the TEAM KP research team in advance on the day and familiarised themselves with the setting before starting video recording tominimise intrusiveness (Parry et al., 2016).

Testing recordings were made first to ensure the equipment is working correctly. The video camera aimed to capture the interaction of the nurse with the participant and the performance of their exercises. Participants had the right to pause or stop the video recording at any point without having to provide any reasons. After the end of each session, the nurse informed PAN that the session is complete and PAN stopped the video recording.

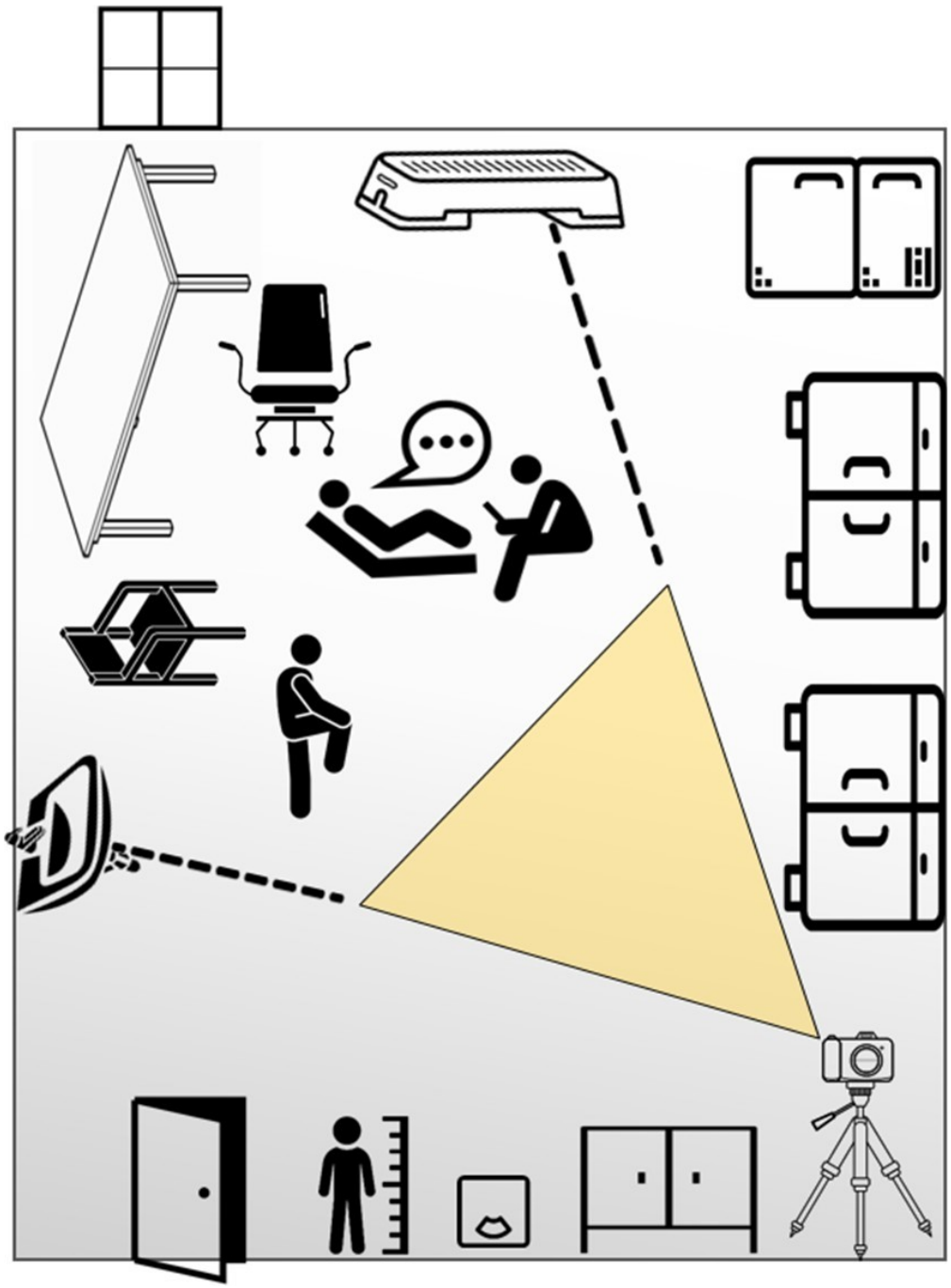


Figure 3—1 Setting the scene in the clinic room

3.4 **Design and stages of data collection**

This is a mixed-methods study. Quantitative and qualitative data were collected and analysed in parallel. During that stage, an interactive approach occurred, that drove changes in the data collection process as proposed by Fetters et al. (2013). The fidelity checklist comprised the quantitative aspect of the study, while the semi-structured interview guides were destined for the qualitative aspect. Fidelity checklists were developed to capture data about the delivery of individual components of the non- pharmacological intervention. These were completed by the nurse and by two researchers independently (PAN, MH), after viewing the video recordings. The semi-structured interview guides were developed to evaluate the acceptability of the non-pharmacological components of the complex intervention. Acceptability is considered as any involvement in the study that will not cause harm to participants, their autonomy will be respected andthe burdens of participating in the study will be outweighed by the benefits of research. The interviews were conducted after the final study visit of the participant.

Following initial data collection, preliminary analysis for the quantitative and qualitative data occurred which led to further refinement in the qualitative and quantitative collection tools. Fidelity checklists were refined through the meetings with the health research team.The interview guides were piloted with independent members of staff, who were given a topic to read regarding knee pain due to OA before the author (PAN) interviewed them.

3.5 **Data analysis**

Fidelity scores were presented as the percentage of components that were delivered as intended for the overall delivery of the intervention, for each session, and for each category and participant. Inter-rater reliability between the two researchers scoring the video recordings was calculated, and the level of agreement between nurse-completed score and researcher-completed (video) score. For delivery of complex interventions such as this, levels of fidelity have been previously interpreted as 'high' fidelity where 80%– 100% of the specified components were delivered as intended, 'moderate' 51%–79%, and'low' 0%–50% (Toomey et al., 2017). Where the fidelity scores are less than 80%, we will explore further to establish which components are responsible.

Qualitative data were sent to an external transcription company. After data transcription,all data were checked for accuracy before transcripts were imported to NVivo V.12.

Qualitative data were analysed using the principles of the general inductive approach (Thomas, 2006) and the framework approach (Ritchie et al., 2003). The former method is convenient, easy to use, does not require an in-depth understanding of a specialist approach, and is strongly associated with focused evaluation questions (Thomas, 2006). The latter method sits within the broad family of thematic analysis but is particularly useful for research that has specific questions and a priori issues that need to be dealt with (Srivastava and Thomson, 2009). The analysis followed the five principles of framework analysis: familiarisation with the data, construction of an initial thematic framework, indexing and sorting the data using the initial thematic framework, finalisation of a thematic framework, and summarising and displaying the data into a matrix. Emergent themes and subthemes were discussed and agreed upon by at least two researchers to increase the validity of the analyses.

3.6 **Data management**

Data were saved onto an encrypted external hard drive for transportation. Each video and audio file was labelled with the project title and a unique code made up of the patient participant identification number, the research nurse participant identification number, the type of camera *eg. LEG/GOP/AUD,* and date. Where there were more than two participants video recorded, the order of numbering for the label was:

- 1st number – research nurse
- 2nd number – participant
- 3rd number – other healthcare professional or student

Recorded data were transferred on the same day from the camera SD card to the University Research drive and then backed up on an encrypted external hard drive. There was a check that the recording played back before the original is deleted from the camera's SD card. Video Recordings were catalogued using a password-protected Excel spreadsheet, which was held on a shared drive and has been anonymised. Data were saved and sent to an external specialist transcription company Transcribe It®. iSkysoft data recovery tool was used to retrieve any data loss.

3.7 **Eligibility Criteria**

Participants eligible for the current study must be:

- Aged at least 40 years
- Able to communicate in spoken English and understand written English
- Self-reporting knee pain on most days of the previous month
- Self-reporting knee pain of at least three months duration
- Self-reporting at least moderate pain on two of the five WOMAC knee paindomains

Participants were excluded if they:

- are housebound or care, home residents,
- are on dialysis or home oxygen
- are pregnant or have dementia
- have a serious mental illness
- have terminal cancer
- have autoimmune rheumatic diseases
- have asthma or COPD requiring regular daily oral corticosteroids
- have unstable angina or heart failure
- have known peripheral vascular disease
- had a stroke with residual weakness or sensory loss
- had physician-diagnosed peripheral neuropathy with sensory or motor deficit

- had previous knee or hip replacement
- are on a waiting list for a knee or hip replacement
- have knee pain rated 8 or above on a 0-10 scale.

Characteristics such as heart failure, severe asthma, peripheral vascular disease, stroke, terminal cancer, may increase the risk of adverse events for those participants and they may not be able to adhere to intervention due to comorbidities and limitations. This pre-specified exclusion criteria will impact the external validity of the study and make the results less generalizable to the entire population.

3.8 **Study Setting**

The intervention was be delivered at Academic Rheumatology, City hospital Nottingham.

3.9 **Informed Consent**

All the participants provided written informed consent. This was obtained by either the research nurse, research fellow (AF), or PAN. A letter to the participants' GP was sent informing them about their participation in the trial.

3.10 **Ethical Approval**

This protocol was approved by the East Midlands-Derby Research Ethics Committee (18/EM/0288) and registered at clinicaltrials.gov (NCT03670706). Any modification to the approved protocol will result in re-submission to gain approval from the REC and study sponsor.

4. Chapter – Fidelity assessment and nurse acceptability

4.1 Introduction

Nurse-led care gives similar or better outcomes than GP-led care for other chronic diseases (Doherty et al., 2018, Saffi et al., 2014, Strömberg et al., 2003, Welch et al., 2010). However, the fidelity of delivery of nurse-led care has not been examined for the management of knee OA.

Fidelity, defined as the degree to which an intervention is delivered as intended (Allen et al., 2012), regulates the relationship between interventions and outcomes and determinesthe extent to which an intervention affects the outcome (Carroll et al., 2007). The concept of fidelity was introduced by Moncher and Prinz (1991) and has evolved. It is categorised into two levels; the theoretical level, which refers to the development and design of the intervention per se, and the operational level that is the extent to which the interventionists deliver treatment following the original plan (Ibrahim and Sidani, 2015). The National Institutes of Health Behaviour Change Consortium (NIHBCC) published a model for fidelity guidance in 2005 (Bellg et al., 2004). The NIHBCC model categorized fidelity in five domains: study design, training of the providers, treatment delivery, treatment receipt, and treatment enactment and provides explanations for each domain. Study design refers to the development and review of a training manual by a panel of experts. The training should be standardised between all the providers and skill acquisitionneeds to be assessed. Treatment delivery involves treatment differentiation, competencyand adherence, while treatment receipt examines if the participant understood the intervention. Treatment enactment uses strategies to assess participants' actual practice of the intervention skills in real-life settings. However, those five behavioural steps developed by Bellg et al. (2004), received criticism by Leventhal and Friedman (2004), and Poltawski et al. (2014) for providing rigid fashioned guidelines. Training of the providers and treatment delivery which require ongoing evaluation and videotaping may be seen as a dictate for provider adherence as a set of behaviours to be delivered rather than adherence to the delivery of the active ingredients (Leventhal and Friedman, 2004).The terminologies used from the NIHBCC "delivery" and "receipt" may be misleading, as they do not suggest that interventions are a dynamic interplay between patient and therapist. They imply that the intervention is a package delivered by the provider and passively received by patient, which is not the case, as it needs to be a co-creation of theintervention in which therapist behaviour affects patient behaviour and vice versa

in orderto negotiate goals (Poltawski et al., 2014).

Fidelity guidelines, therefore, were updated in 2011. (Borrelli, 2011). Strategies using fidelity with flexibility are recommended and a more flexible approach has been adopted within each of the domains. Although training of the providers needs to be standardised, flexible adaptation to different learning styles and providers' levels of experience has to be considered. It is concluded that planning fidelity may require extra staff and costs; however, the economic and scientific costs of lack of treatment fidelity overcome the costsof fidelity implementation. A five-point Likert scale has been suggested by Borrelli (2011),to rate the items on the developed measurement rather than a dichotomous scale. Although the NIHBCC model is developed to be used in psychologically-focused interventions it is now evident in physical rehabilitation research (Poltawski et al., 2014).A review (Ibrahim and Sidani, 2015), highlighted the need to develop measures of fidelity assessment with acceptable psychometric properties that will be relevant and can be adapted to the target population. The FRESH study (Radford et al., 2018) was a multicentre (three sites) feasibility randomised controlled trial (RCT) to evaluate the fidelity of trained occupational therapists (n=4) delivering treatment for traumatic brain injury. The intervention was delivered with high fidelity apart from the component "progress monitoring". The SOLAS feasibility trial (Toomey et al., 2017), assessed the fidelity of physiotherapists (N=9) delivering OA and chronic low back pain intervention across seven sites. The intervention was delivered with high fidelity. Those studies increased the power to detect effects and reduced the random variability of treatment delivery. Inferences regarding the treatment effect of a complex intervention should therefore not be made without assessing fidelity, because lack of efficacy of an intervention may be due to inadequate implementation (Moncher and Prinz, 1991). Thus, the fidelity of intervention delivery influences the internal and external validity of a study (Colditz and Emmons, 2012). If fidelity is not assessed, effective interventions may be rejected due to poor delivery (Borrelli, 2011, Walker et al., 2017). Delivering care according to provider treatment preferences is of clinical importance and aids patient adherence, satisfaction with treatment, and outcome achievement. Similarly, practitioners only implement an intervention as intended if they find it acceptable to deliver (Borrelli et al., 2005). Whether the nurse delivering such diverse interventions would find it acceptable to do so is still not known.

There are several methods to assess treatment fidelity, including direct observation, patient self-

report questionnaire, provider self-report checklist, and indirect observation using audio or video-recordings (Borrelli, 2011), which may be used singularly or in combination. Direct observation is considered the gold standard, however, it can be intrusive and may affect patient-practitioner interaction (Bellg et al., 2004, French et al.,2015), and may not be feasible in large RCTs. Provider self-report methods are simple and inexpensive but can be inaccurate (Jobe, 2003), and patient report methods are even lessreliable (Borrelli, 2011). Video-recording the delivery of the intervention and independentassessment of fidelity may provide a robust alternative to direct observation (Schulte et al., 2009). Indeed (Huijg et al., 2015, McKenna et al., 2014), it has been shown previously that assessing fidelity using independently rated recordings and provider self-report checklist is feasible and acceptable (Toomey et al., 2016). A combination of provider self-report and independently assessed video recording was utilised in the current study to provide an in-depth fidelity assessment. (Toomey et al., 2017). Video recordings were chosen, as this is less intrusive than direct observation and provides an opportunity to assess reliability. The pros and cons of each method used for fidelity assessment are highlighted in Table 4—1.

Table 4—1 Pros and cos of the methods used to assess fidelity

Method	Pros	Cons
Audio recording	Objective evaluation Listen to previous visits	Slightly obtrusive
Video recording	Evaluation of non-verbal communications	More obtrusive and costly
Provider self-report (checklist)	Cues providers implement treatments with fidelity Allows comparison with other methods Inexpensive	Provider time-consuming Providers rate themselves more adherent
Direct Observation	More accurate than self-report, but less than video recording	"Reactivity effects" by the practitioners

MRC guidelines for developing and evaluating complex interventions (Craig et al., 2008) have highlighted the importance of conducting a process evaluation. Its' purpose is to assess the quality and quantity of the implementation of the intervention, and trials that collect rich qualitative data may identify potential barriers and facilitators to intervention implementation. However, collecting only qualitative or quantitative data to assess treatment delivery would not unearth a comprehensive picture to understand complex constructs within the intervention (Farmer et al., 2006). For this reason, a mixed-methods approach was utilized (Moore et al., 2015a).

The systematic review in chapter 1 indicated very poor reporting of fidelity of delivery of non-pharmacological interventions for knee pain due to OA. The present study is part of the East-Midlands Knee Pain Cohort RCT study, (Hall et al., 2020) the overall purpose of which is to evaluate the feasibility of a nurse-led package of care for knee paindue to OA. The objective of the present study was to evaluate the fidelity of delivery of a nurse-led non-pharmacological package of care for knee pain and explore the experiences of the nurse in delivering the intervention, and resolve possible challenges to future delivery during the package development phase of the RCT.

4.2 Methods

4.2.1 Study Design

A mixed-methods study with an explanatory sequential and convergent design. This form of mixed methods approach was used to produce additional insights into the issue at hand.In this design, qualitative and quantitative data are collected and complementary results arise from the use of different methods (FLICK, 2014). In the current study, the quantitative data informed the collection of qualitative data and a convergence approach was followed.

4.2.2 Setting

Academic Rheumatology, City Hospital Nottingham.

4.2.3 Participants and Recruitment

The participants were adults self-reporting knee pain and the research nurse. Community-dwelling adults participating in the IMHW cohort (Millar et al., 2020), self-reporting knee pain were sent a postal invitation to participate in this study. People who responded underwent telephone screening to assess eligibility. Section 3.2 provides more detail about the eligibility of the study.

4.2.4 Research nurse training

A training programme to enable a nurse to deliver the current NICE guidelines for OA management was developed and an educational manual was produced (Hall et al., 2020). The nurse delivering the intervention was working as a research nurse previously and did not have prior knowledge of musculoskeletal diseases, had not worked in rheumatology or allied specialties such as orthopaedics, rehabilitation, or sports medicine, and had never delivered treatments for arthritis. Section 3.1 describes the details about the content of the training.

4.2.5 Patient and Public Involvement

Three PPI members with hip and/or knee OA provided input into the content of the non-pharmacological treatment package and volunteered for nurse training. They advise that video recording of treatment sessions would be acceptable to participants. They also advised us that they would not prefer the nurse to be asking about adherence quite often as patients might feel overburdened by filling in the activity diary twice a day. For these reasons, the nurse enquired about adherence only at the follow-up visit.

4.2.6 Intervention

The TIDieR checklist (Hoffmann et al., 2014) has been used to describe the intervention and its key features (Table 4—2). In brief, the intervention consisted of a holistic assessment of the participant, providing education about the nature of OA and self- management strategies including advice on the role of exercise, maintaining a healthy weight, and use of adjunctive treatments such as application of heat or cold, foot-wear modification and use of walking aids At the first visit, the nurse took a medical history, examined the knee joints, and explained to the participant that they had knee pain due toOA. Investigations and radiographs were not undertaken as per NICE guidelines. The Chief Investigator (AA) was available for advice if a clinical diagnosis of OA could not be reached. In that case, the participant would be deemed ineligible for the study. All participants were given an Arthritis Research UK leaflet on knee OA. The nurse explained aerobic and strengthening exercises and advised each participant on an individualised regimen that was mutually agreed. If required, weight-loss advice was provided. Behaviour change strategies (Michie et al., 2008) such as goal setting, action planning, assessment of participant confidence to achieve goals, discussion of barriers and facilitators, and the use of exercise diaries were used to improve adherence. Functional goals were agreed upon and were used to facilitate the exercise prescription with goals being Specific, Measurable, Achievable, Relevant, and Timely (SMART). SMART weight loss goals were agreed also upon with overweight participants. The intervention is described in more detail in the protocol (Hall et al., 2020). After the training period, the nurse delivered the intervention in four sessions over five weeks.

Table 4—2 Items of the non-pharmacological intervention

1. Brief name	Non-pharmacological complex intervention comprised of education, exercise, and weight loss advice if required.
2. Aims and Rationale	Development and evaluation of the non-pharmacological treatment component.
3. What was done?	Training package of the provider: The content of the package was based on NICE guidelines for the management of OA and a report by Arthritis Research UK on the educational needs of health professionals working with people with OA. The content consisted of a standardised treatment manual. Academic and clinical experts and members of a patient advisory group have provided input into the training package. Their key components were: • The epidemiology and nature of knee pain and knee OA • Assessment of the patient with knee OA • Core NICE guidelines for managing OA • Principles of strengthening and aerobic exercise prescription for knee OA

	• Information and advice to support weight loss • Strategies to support behaviour change • Pharmacological management of OA and knee pain following a step-wise protocol of optimising analgesia Mode of delivery: Four face-to-face individual sessions over a five-week period.
4. Who delivered the intervention ?	A trained nurse with no prior knowledge of treating musculoskeletal conditions delivered the non-pharmacological intervention to knee pain people. A rheumatologist and research physiotherapist delivered in total eight sessions of the module over a three-month period.
5. Where was the intervention provided?	Single centre research setting, clinic room, city hospital, Nottingham
6. When and how often or how much of the intervention was provided?	The complex intervention was delivered for up to 1.5 hours in session one and 46 minutes in the follow up sessions. The nurse was endeavoured to provide as much intervention as an individual could tolerate. The amount of the intervention was video recorded.

7. Was the intervention tailored?	Tailoring was built in the intervention. Functional goals were agreed between the nurse and people with knee pain to facilitate exercise prescription. Weight loss goals were agreed with patients who were overweight. The description of the treatment manual highlights procedures for tailoring practice activities. No modifications of the intervention were made during the course of the study.
8. How well was the intervention delivered?	A single research nurse who received training, delivered the intervention and fidelity was assessed by video recording all sessions. After preliminary fidelity analysis, the nurse received additional supervised training to deliver the intervention.

4.2.7 Ethical approval

The study received ethical approval from the East Midlands-Derby Research EthicsCommittee (REC) (18/EM/0288).

4.2.8 Consent

All study participants including the research nurse gave their written informed consent before treatment delivery, including the consent to video record the sessions. Participants had the right to pause or stop the video recording at any point without giving any reasons.

4.2.9 Fidelity assessment

The study followed the NIHBCC guidelines for fidelity assessment (Borrelli, 2011). The fidelity checklist was developed a priori (Hall et al., 2020) and comprised eight components, each with specific tasks: materials; introduction; assessment; education; exercise; weight loss; advice on adjunctive treatments; and review and planning (Table 4—3).

Table 4—3 Fidelity checklist of the non-pharmacological component of intervention

Session 1: **Intervention categories individual components**	Completed	Not completed	Partially completed	Not applicable
Materials				
ARUK booklet on OA				
Exercise/activity diary				
Goal Setting forms				
Introduction				
Introductions				
Aim of interventions				
Content				
Structure				
Holistic assessment of person with OA.				
Illness perception of OA explored				
Pain severity explored				
Pain impact on occupation or social activity explored				
Current level of physical activity/ exercise and its intensity explored				
Views and attitudes to weight loss explored (if required)				
Issues with mood explored				
Sleep quality explored				
Support network and caregiver involvement discussed				
Co-morbidities				
Other MSK pain				
Inspection of knee				
Palpation of knee				
Active ROM				
Passive ROM				
Observation of Gait				
Education				
Illness perception of OA addressed				
Nature of OA discussed				
Core treatments for OA addressed				
Rationale for self-management strategies addressed				
Physical Activity /benefits of exercise addressed				
Activity rest cycle/pacing explained				
Reflection on activity/pacing and recommendations discussed				
Participants had the chance to contribute to discussion				
Exercise				
Warm up exercises explained/demonstrated				
Aerobic exercises explained/demonstrated				
Strengthening explained/demonstrated				
Stretching exercises explained/demonstrated				
Participants had the chance to practice prescribed exercises				
Exercise corrected if required				
Smart goals setting				
Action planning to carry out exercise				
Patients' level of confidence for the exercise programme determined				
Barriers and facilitators identified (if confidence low)				
Weight loss (if required)				
Previous efforts to lose weight discussed				

Healthy BMI range and weight loss discussed				
5% weight loss goal calculated with timescale				
Agree weight loss goal				
Action plan for weight loss				
Discuss strategies for weight loss (calorie deficit, portion size, meal planning, tops tips, slimming groups, increasing PA etc)				
Signpost to NHS weight loss plan				
Patients' level of confidence for weight loss goal determined				
Barriers and facilitators identified (if confidence low)				
Adjunct treatments				
Use of heat/cold discussed				
Walking aids discussed				
Footwear discussed				
Review and planning				
Session review: goal setting synopsis and action plan				

Completed = component was fully delivered by the nurse
Not Completed = component was not delivered by the nurse
Partially completed = there was an attempt to deliver this component by the nurse but it was not delivered fully
Not applicable = component was not applicable for example weight loss components if the participant had a body mass index < 25

Follow up session 2, 3: **Intervention categories individual components**	Completed	Not Completed	Partially completed	Not applicable
Assessment				
Pain symptoms since previous visit explored				
Factors influencing pain explored				
Physical activity's levels explored				
Education				
Activity rest cycle/pacing explained				
Individual reflection on activity-rest cycle/pacing facilitated				
Physical activity's levels addressed				
Participants had the chance to contribute to discussion				
Exercise				
Exercise goals and action plan reviewed				
Exercise/activity diary reviewed				
Problem solving of previous weeks action plan				
Previous session exercises reviewed and performed by the participant				
Exercise corrected if required				
Smart goals reviewed				
Strengthening exercises progressed or adapted				
Aerobic exercises progressed or adapted				
Participants had the chance to practice strengthening exercises				
Patients' level of confidence for the exercise programme determined				
Barriers and facilitators carrying out the exercise identified(if confidence low)				
Weight loss (if required)				
Weight loss goal and action plan reviewed				
Weight reviewed				
Action plan updated				
Patients' level of confidence for weight loss goal determined				
Barriers and facilitators identified (if confidence low)				
Adjunct treatments				
Use of heat/cold discussed				
Walking aids discussed				
Footwear discussed				
Review and planning				
Session review: goal setting synopsis and action plan				

Final session: Intervention categories individual components	Completed	Not completed	Partially completed	Not applicable
Assessment				
Pain symptoms since previous visit explored				
Factors influencing pain explored				
Physical activity's levels explored				
Education				
Long-term self-management addressed				
Participants had the chance to contribute to discussion				
Exercise				
Exercise goals and action plan reviewed				
Exercise/activity diary reviewed				
Problem solving of previous weeks action plan				
Participants had the chance to attempt and practice previous exercises				
Exercise corrected if required				
Patients' level of confidence for the exercise programme determined				
Barriers and facilitators carrying out the exercise identified (if confidence low)				
Exercises aiming for long term management given				
Weight loss (if required)				
Weight loss goal and action plan reviewed				
Weight reviewed				
Action plan updated				
Patients' level of confidence for weight loss goal determined				
Barriers and facilitators identified (if confidence low)				
Long term action plan for weight loss given				
Review and planning				
Session review – long term goal setting and action planning recap				

However, not all components of the intervention were intended to be delivered in each session (Hall et al., 2020). For example, advice on adjunctive treatments could be provided in any of the four sessions. The fidelity checklist was iteratively developed using a five-step methodology (Walton et al., 2020). These were: reviewing previous measures, analysing intervention components and developing an intervention framework (intervention manual), developing the fidelity checklist, obtaining feedback about the content and wording of the checklist, and piloting and refining the checklist to assess and improve reliability. The latter stage occurred after collecting data from six participants, where the researcher (PAN) and the nurse rated twenty-two sessions using the initially developed fidelity checklist. The nurse and the researcher assessed treatment delivery and implementation of the non-pharmacological intervention and preliminary analysis occurred. Regular meetings with the intervention developers took place and resulted in the refinement of the initial fidelity checklist. In line with feedback received from AA and MH, adjustments were made to minimise

the jargon. As a result, we further clarified the content of the sessions; unclear terminologies such as *"set clear expectations"*were removed and the components of the categories have all been organised better. For example, the component *"action planning introduced"* existed within the education category rather than the exercise or weight loss category. As there was a need for the participants to have an action plan to perform their exercises and follow the weight loss advice, we have moved the "action planning" component to the exercise and weight loss categories. The responses of the fidelity checklist were categorical and rated as completed,partially completed, not completed, or not applicable. Partially completed scores were given for any task that was not delivered to the full extent in the context of that particularconsultation. The scoring criteria of the fidelity checklist followed that of previously published strategies for assessing fidelity in RCTs of complex interventions (Ang et al., 2018). After conducting regular meetings with the health research team, we have discussed and agreed that the exercise category should be delivered in each session compared with the adjunct treatments and the education that should be included in at least one session. Therefore, we have agreed that if the nurse addresses the components of the adjunct treatments or the education in at least one of the sessions that is considered as completed, and the components are delivered.

Eighteen participants received the non-pharmacological intervention. Of these, fourteen completed all four visits and all sessions were video-recorded (n=62). The reasons for dropping out were other commitments (n=2), reluctance to lose weight (n=1), and inadequate understanding of the nature of the intervention (n=1). After every session with the participant, the nurse completed the fidelity checklist. Sixty-two checklists, 18 for session 1, 16 for session 2, and 14 each for sessions 3 and 4 were completed. Blinded to the nurse ratings, the video-recording of every session was independently reviewed and rated by PAN. A second-rater(MH) independently rated 20% (n=12) of the sessions. Both raters were familiar with the intervention. The refinement, reliability, and feasibility of the fidelity checklist was established during the initial phases of the data collection process.

4.2.10 Quantitative data analysis

Mean and SD, median and IQR, and n (%), were calculated for descriptive purposes. Withina component, tasks rated as 'completed' were given a score of 2, 'partially completed' a score of 1, and not completed, a score of zero. To obtain a fidelity score for a component of the intervention, individual scores for each task within the component were added and divided by the maximum possible score for that component and converted to a percentage. Any tasks that were rated as not applicable, were excluded from the calculation.

Median fidelity scores (%) and IQR were calculated for the entire intervention, per participant, per session, and a component of the intervention. Fidelity was classified as previously reported: 80-100% 'high', 51-79% 'moderate', and 0-50% 'low' fidelity (Borrelliet al., 2005). Where fidelity was moderate or low in a particular component, we further explored this by examining the fidelity of delivery of the individual tasks.

Percentage agreement with 95% CI was used to estimate the level of agreement betweenself-report and video-record methods, and for inter-rater agreement.

4.2.11 Qualitative phase

One week after the final session, the research nurse was approached by PAN to participate in an interview. The nurse took part in a semi-structured interview conducted by PAN and AF. An additional interview was conducted via video call with the nurse after initial data analysis 45 weeks later, to explore any gaps or areasof uncertainty. The interview guide (Appendix VI) contained open-ended questions developed by the study team, which included a rheumatologist (AA), physiotherapists (MH, PAN), psychologist (RdN), and qualitative researcher (AF). The guide covered the nurse's views on their training, views and experiences of delivering the non-pharmacological intervention; confidence in delivering the individual components of the non-pharmacological intervention, perceived barriers to delivering it as planned, and opportunities to improve the non-pharmacologicalpackage of care. An iterative process was used for data collection, so an additional interview was conducted 45 weeks later to capture any salient points raised from the initial quantitative and qualitative data collected. The salient points refer to data regarding the adjunctive treatments and goal setting that could not be captured at the first instance.

Before starting the interview, it was explained that the nurse's responses would remain confidential and that any quotes included in future publications would not identify them. The nurse was informed of the right to withdraw from the interview at any time. We have not provided demographic details to protect the anonymity of the individual nurse. All interviews were conducted in a private room in Academic Rheumatology, City Hospital, Nottingham. The qualitative findings were mapped onto the fidelity checklist to assess convergence between the quantitative and qualitative findings. Any areas of uncertainty or gaps were then explored in the second interview with the nurse. Areas of uncertainty included

4.2.12 Qualitative data analysis

The interviews were transcribed verbatim by an external transcription company. The interviewer removed any identifiers and ensured transcripts were accurate. Transcripts were analysed following the principles of the general inductive approach (Thomas, 2006).The latter is a simple straightforward approach, which is used to derive findings from raw qualitative data, condense them into a brief summary format, and link the research objectives with the summary findings. Inductive research begins with collecting empirical data and observations (Ritchie et al., 2003). It is the process by which data are being drawn to a general conclusion from individual instances / observations and differs from a deductive approach as the latter seeks to draw conclusions from initial premises.

The first transcript was read several times before data related to the research objectives were identified, labelled and categorised. The categories were discussed between the interviewer and a second researcher (AF). This process identified gaps and led to the second interview and the transcript was analysed in the same way. Following agreement that the categories reflected the overall account reported by the nurse, extracts were taken from the transcripts to exemplify the findings.

4.2.13 Convergence of the findings

A meta-matrix was developed to explore the convergence between the findings. This deductive approach enhances study validity by increasing the probability that our findings and interpretations are credible and reliable (Farmer et al., 2006). Convergence was defined as an agreement between both sets of data, and discrepancy as a disagreement between them.

4.2.14 Reporting guidelines

The Standards for Quality Improvement Reporting Excellence (SQUIRE) guidelines (Ogrinc et al., 2016) were used to improve the quality of reporting of this study.

4.3 Results

4.3.1 Quantitative findings

Eighteen participants (33% women) with knee pain for longer than 3 months, with a mean age of 68.7 (SD 9.0) years and BMI of 31.2 (SD 8.4) kg/m^2 respectively took part in the study.

In total, 62 intervention sessions were delivered. The median (IQR) duration of the initial and follow-up sessions was 87 (81–101) and 46 (37–52) minutes respectively. Overall fidelity was rated high for both nurse self-report (97.7%) and video-rated scores (84.2%) (Tables 4-4, 4-5). Inter-rater agreement for the video-recording checklist was 70.3% (95%CI 64.4, 74.2).

For the nurse self-report checklist, median fidelity scores for each session ranged from 94.4-100% (Table 4—4). Individual components received high ratings except for adjunctive treatments i.e. use of heat/cold therapy and advice on footwear where the fidelity score was moderate in many sessions.

Table 4—4 Nurse self-reported fidelity scores[1]

Intervention component	Session1 (n=18)*	Session 2 (n=16)*	Session 3 (n=14)*	Session 4 (n=14)*
Materials	100 (100, 100)	-	-	-
Introduction	100 (100, 100)	-	-	-
Assessment	100 (98.3, 100)	100 (100, 100)	100 (100, 100)	100 (100, 100)
Education	100 (100, 100)	100 (100, 100)	100 (100, 100)	100 (100, 100)
Exercise	100 (97.5, 100)	100 (100, 100)	100 (97.5, 100)	100 (75, 100)
Weight loss	100 (88.9, 100)	100 (100, 100)	100 (66.7, 100)	100 (79.2, 100)
Adjunct treatments	87.5 (33.3 100)	87.5 (0, 100)	66.7 (45.8, 100)	-
Review and planning	100 (100, 100)	100 (100, 100)	100 (100, 100)	100 (100, 100)

[1]Values are median% (IQR)

*Number of sessions

For the video-rated checklists, overall median fidelity scores for each session ranged from 77.7-87.2% (Table 4—5). Fidelity for education was lower in the first session (78.1%, IQR74.1, 93.8) but increased in the follow-up session (87.5%, IQR 50,100). Fidelity for reviewand planning was lower in the first and last sessions. Fidelity scores were low for adjunctive treatments across all sessions and varied from 0% to 50%. Fidelity of delivery for exercisegoal-setting was moderate at 66% and, fidelity for reviewing goals during follow-up sessions was low, ranging between 44-50%. Additionally, the assessment of patient's level of confidence to achieve their exercise goal was low in the follow-up sessions, ranging between 7-40%.

Table 4—5 Fidelity scores using video-recordings of the sessions[1]

Intervention Component	Session 1 (n=18)*	Session 2 (n=16)*	Session 3* (n=14)*	Session 4 (n=14)*
Materials	100 (100, 100)	-	-	-
Introduction	100 (75, 100)	-	-	-
Assessment	91.4 (85, 93.3)	100 (100, 100)	100 (100, 100)	100 (100, 100)
Education	78.1 (74.1, 93.8)	87.5 (50, 100)	87.5 (50, 100)	100 (93.8, 100)
Exercise	94.4 (88.9, 100)	88.9 (75, 94.4)	86.1 (72, 100)	75 (67.6, 82.8)
Weight loss	100 (87.5, 100)	90 (60, 100)	100 (68.9, 100)	80 (49.2, 100)
Adjunct treatments	50 (45.8, 100)	0 (0, 50)	50 (0, 100)	-
Review and planning	75 (75, 100)	100 (100, 100)	100 (100, 100)	75 (37.5, 100)

[1]Values are median% (IQR),

*Number of sessions

The overall agreement between nurse-rated and video-rated methods was 73.3% (95% CI 71.3 - 75.3). The level of agreement for individual components is shown in Figure 4—1. Excellent agreement was found for materials, introduction, and assessment. The agreement was below the cut-off point of 80% for education, exercise, weight loss, and adjunctive treatment. The level of agreement for the review and planning component was 58.1% (95% CI 44.8, 70.5).

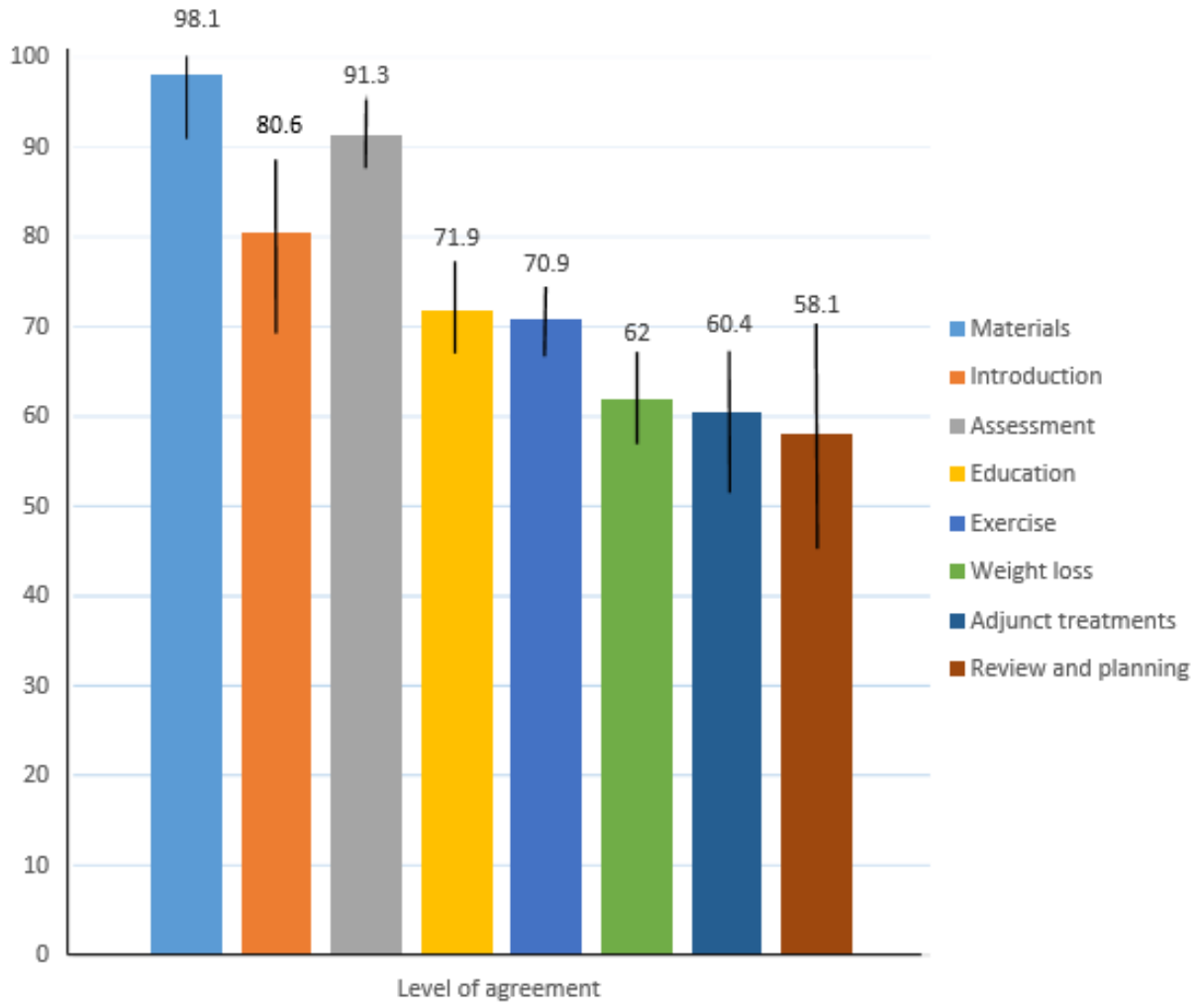


Figure 4—1 Agreement between nurse-rated and video-rated methods for the components of the intervention Values shown are % agreement and error bars indicate the 95% CI

For individual participants, overall fidelity across the four sessions ranged from 75% to 100% indicating that for most patients the intervention was delivered as intended (Table 4—6).

Table 4—6 Fidelity scores assessed using video-recordings across participants[1]

Participant number	All sessions
Participant 1	88.9 (75, 100)
Participant 2	83.3 (41.7, 100)
Participant 3	100 (67.5, 100)
Participant 4*	96.7 (88.9, 100)
Participant 5	75 (45, 100)
Participant 6	100 (80, 100)
Participant 7	100 (89.9, 100)
Participant 8*	100 (95.8, 100)
Participant 9	92.9 (50, 100)
Participant 10	93.7 (77.5, 100)
Participant 11*	75 (50, 97.2)
Participant 12	73.8 (18.8, 100)
Participant 13	100 (67, 100)
Participant 14	100 (79, 100)
Participant 15	85 (56, 100)
Participant 16	100 (75, 100)
Participant 17	100 (80, 100)
Participant 18*	100 (81, 100)

[1]Values are median% (IQR)

*Participants dropped out. The percentage fidelity score is calculated using scores from the sessions attended.

Following the inspection of the video-rated scores, fidelity for education and exercise categories was moderate in the first session (78.1%, IQR 74.1, 93.8) and the fourth session (75%, IQR 67.6, 82.8), and fidelity scores were low for adjunctive treatments across all sessions. Therefore, we have broken down the fidelity of those categories. The purpose of this was to use the results, and improve the delivery of intervention so we would be aware of what brought these scores down and further boost nurse's training. We have, therefore, calculated the frequencies of those components that the nurse is not delivering expressed as percentages. For the analysis of this particular dataset, "partially completed" scoring criteria were considered as "not completed" and N/A data have been omitted from the analysis. The specific tasks of the individual components of the categories that the nurse is not delivering have been identified (*Table 4—7* & *Table 4—8* & *Table 4—9*) and are mentioned below:

Table 4—7 Individual components (%) of the education category the nurse is not delivering

Education components	*Session 1*	*Session 2*	Session 3
Illness perception of OA addressed	11%	-	-
Nature of OA discussed	5.5%	-	-
Core treatments for OA addressed	39%	-	-
Rationale for self-management strategies addressed	75%	-	-
PA /benefits of exercise addressed	6%	25%	-
Activity rest cycle/pacing explained	38.5%	58.3%	-
Reflection on activity/pacing and recommendations discussed	14%	36%	-
Participants had the chance to contribute to discussion	0%	0%	0%
Long-term self-management addressed	-	-	21.5

Table 4—8 Individual components (%) of the exercise category the nurse is not delivering

Exercise components	*Session 1*	*Session 2*	*Session 3*	*Session 4*
Warm up exercises explained/demonstrated	22%	-	-	-
Aerobic exercises explained/demonstrated	0%	-	-	-
Strengthening explained/demonstrated	0%	-	-	-
Stretching exercises explained/demonstrated	34%	-	-	-
Participants had the chance to practice prescribed exercises	0%	-	-	-
Exercise corrected if required	5%	6.7%	15%	15%
Smart goal setting	34%	-	-	-
Action planning to carry out exercise	11%	-	-	-
Patients level of confidence for exercise programme determined	6%	62.5%	60%	93%
Barriers and facilitators carrying out the exercise identified	5%	37.5%	75%	58.3%
Exercise goals and action plan reviewed	-	25%	15%	29%
Aerobic exercises progressed or adapted	-	23%	38%	-
Strengthening exercises progressed	-	0%	7%	-
Previous session exercises reviewed and performed by participant	-	0%	0%	-
Participants had the chance to practice strengthening exercises	-	6.3%	15%	15%
Smart goals reviewed	-	56%	50%	-
Exercise/activity diary reviewed	-	19%	0%	15%
Problem solving of previous weeks action plan		0%	0%	7%

Exercises aiming for long-term management given	-	-	-	23

Table 4—9 Individual components (%) of the adjunct treatments the nurse is not delivering

Adjunct treatments	*Session 1*	*Session 2*	*Session 3*
Use of heat/cold discussed	23%	58%	42%
Walking aids discussed	55.5%	100%	75%
Footwear discussed	50%	79%	60

4.3.2 Qualitative Findings

The duration of the initial and follow-up interview with the nurse was 94 minutes, and 34 minutes respectively.

Nurse's barriers to deliver the package

Barriers to deliver the package of care as intended were identified by the nurse. Barriers comprised lack of resources (e.g. laptop), *"Laptop should have been there in the room or computer" (KPS0001),* which meant that the nurse could not search for other online sources while treating patients and had difficulty calculating the BMI. Other barriers were:not enough space in the clinic room to perform a knee assessment, and patients not beingadvised by the staff to wear shorts in the first session, which meant that the nurse was unable to assess their knees properly. *"There was not much room in the, in that room to,to have your all the resources laid out". "Was not enough room so should have been helpfulto have a little bit bigger room and then I haven't had to move step around the room fromhere to there, that would have been helpful (KPS0001).*

The nurse reported feeling nervous when delivering the intervention for the very first time but felt more comfortable as the sessions progressed.

"Very nervous… to start with... I don't think after a few sessions I was uncomfortable, I was probably more comfortable delivering the intervention…after few sessions, got better at getting feedback from patient as well so I think that boosted my confidence".

The nurse felt that patient assessment was easy to deliver considering their previous experience of assessing patients for other diseases.

"I would say some of them were easy to find pinpoint the problems…as a nurse, we always been asking these questions to patients… in this case but had previous experience in that area"

The nurse felt that education was not always delivered as well in the first few sessions as

in the follow-up sessions. They felt that there was a lot of information for the participants to take on board during that first initial assessment session and recommended that the advice could be spread over two or three sessions.

"First few sessions I didn't think of as very good to tell them about the information and then later on, I built that …"

"I think that session could be divided, erm, the very first one at least in two sessions… so first session, you just get to know the patient and they get their feedback and, don't give them any, too much of a diet and weight loss information"

The nurse described how they initially lacked confidence in prescribing exercise, which was a new skill, to the patients.

"I had to decide after the assessment which exercise I'm going to assign them and I didn't feel comfortable…"I wasn't sure that whatever assessment I have done and the exercise I choose, that's going to make it any better ... I wasn't 100% sure".

On the other hand, it was easier to determine and link the exercises for patients who already had obvious problems in their knees.

"When there are obviously problems in the knee you can see, you can link what exercise… when you can't see the obvious problems, then it was difficult to determine what exercise you are going to assign"

They felt more confident and were able to adapt the exercises as they became more familiar with the exercises and having received feedback from the patients.

"I felt comfortable altering the exercise for them,… knowing that obviously, if it's painful for them then switching to a different exercise."

The nurse delivered the weight loss advice with ease compared with the exercise and was able to explain to patients why it is good to lose weight where required.

"For the weight loss, you easily do that... I didn't feel too much uncomfortable…so positive from that is that I managed to tell everyone."

Even though they felt it was not difficult to deliver or incorporate the adjunctive treatments, they occasionally forgot to mention them or felt it was not necessary to repeat this in a subsequent session.

"I do not think it was difficult to ask that or incorporate… it was probably as a human error or that you forgot to mention it…with some patients if you already mentioned once or twice, so with the first session, that if you need to you can use hot and cold therapy, and then they refuse it … then there is no point [mentioning it again]"

The nurse found it challenging to negotiate realistic goals with some patients, especially those who had high expectations but rated their confidence in achieve their goals as low.

"The difficulty is that the goal setting they would expect high but then they when you ask them how likely you are going to achieve this goal their rating will be low… their rating will be like 4 or 5 and how you motivate them to go up to 8 or 7, 8, 9, that one's kind of difficult."

However, the nurse was able to reduce the expectation that was initially set for that particular goal for those patients.

"Obviously there was a previous goal…yes would reduce the expectation when they came back, I would be able to do this, so I am sure you would be able to see through the videotape"

4.3.3 Integrating the findings

Convergence was found between the fidelity scores and nurse interviews (Table 4—10). The excellent fidelity scores for the holistic assessment by the nurse was reflected in their confidence in assessing patients more generally. The moderate fidelity findings for education in the first session that increased in subsequent sessions was confirmed by the nurse and explained in terms of moderating the amount of information that was given to participants in the first session. Weight loss advice was delivered with high fidelity and the nurse also felt confident in being able to deliver weight loss advice fully. A perceived lack of confidence in delivering the exercise component is consistent with lower fidelity scores for the exercise component. The adjunctive treatments were not always delivered as intended and that was consistent with the interview findings. Goal setting was challenging for the nurse which was reflected in the fidelity findings. Finally, convergence was found for review and planning as the nurse found it easy to summarise patient goals at the end of each session. There were no divergent findings.

Table 4—10 Convergence between fidelity observed using video recordings and the results from the semi-structured nurse interview

Intervention components	**Median (%) IQR fidelity ***	**Qualitative interview findings**	**Convergence**
All components	*84.2*	*" I find myself that … that I can deliver the care…I was probably more comfortable delivering the intervention…after few sessions"*	Yes
Materials	*100 (100, 100)*	*" I had to show them the booklet every patient so I don't think I have forgotten to do that"*	Yes
Introduction	*100 (75, 100)*	*"I explain all the study and then explain that whole process again for the purpose of the session"*	Yes
Assessment	*100 (100, 100)*	*"I would say some of them were easy to find pinpoint the problems…as a nurse we always been asking these questions to patients… in this case but had previous experience in that area"*	Yes
Exercise	*88.9 (72.7, 94.4)*	*"We practiced and demonstrated exercises… I felt comfortable altering the exercise for them…I just couldn't think how to link that, erm, goal setting I didn't deliver it good… I don't think I could have delivered it any better than that either… some did actually achieve the goal"*	Yes
Education	*87.5 (74.1, 100)*	*"first few sessions I didn't think of as very good to tell them about the information and then later on, I built that"*	Yes

Weight loss	*100 (77.8, 100)*	*"Positive from that is that I managed to tell everyone that, "you need to lose weight", so I think it was kind of structured in a way… I didn't feel too much uncomfortable"*	Yes
Adjunct treatments	*50 (0, 50)*	*"it was probably as a human error or that you forgot to mention it…with some patients if you already mentioned once or twice so with the first session that you need to you can use hot and cold therapy and then they refuse it and then there is no point"*	Yes
Review and planning	*100 (25, 100)*	*"Not difficult… we always talked about it this is what we discussed it today this is the exercise we, have assigned you and if you feel that you can progress into further do so"*	Yes

*Median fidelity scores of the individual components across the four sessions

4.4 Discussion

This study evaluated the fidelity of delivery of a nurse-led non-pharmacological package of care for knee pain due to OA and validated the findings in an interview with the nurse that delivered it. The majority of the non-pharmacological components of the intervention were delivered with good fidelity. Excellent fidelity was found for patient assessment, education, demonstration, and advice on exercise and weight loss advice. Tasks that demonstrated lower fidelity within the exercise component included goal setting and review. These were also perceived as difficult by the nurse. Advice around the use of adjunctive treatments such as the use of hot or cold treatments, walking aids and footwear, were also not always delivered as planned. Agreement between the nurse and independent rater was below the cut-off point of 80% for education, exercise, weight loss,adjunctive treatment, and review and planning, which is reported as the minimum acceptable agreement between raters (McHugh, 2012). Fidelity scores across different participants were high overall with the lowest score being 74%.

To the authors' knowledge, this is the first study that has assessed fidelity of a nurse-lednon-pharmacological intervention for knee pain due to OA and integrated the findings. Ourstudy is based on a fidelity checklist that has been previously validated in complex interventions delivered in a research setting (Toomey et al., 2016). We tailored the checklist according to the intervention and further refined it. Moreover, the reliability of the fidelity checklist was established when two independent viewers scored the video recordings of the sessions.

From the interview transcripts, factors that influenced the fidelity of delivery are identified.The nurse was less confident to identify appropriate patient goals and prescribe exercise in the first few sessions, but this improved thereafter. This is not a barrier per se but suggests that some further training and additional support for nurses in this new role would be needed to ensure fidelity at the start of the study. The nurse was able to draw on her previous experience working with other patient groups to discuss and assess

complex issues. Nurse's previous experience assessing patients, therefore, facilitated fidelity of delivery. Although the fidelity for education appeared to be lower in the first session this was because the nurse recognised and responded that participants were beinggiven a lot of information. These findings are not surprising as we aimed to train a nurse with no prior experience in managing musculoskeletal diseases to deliver a complex non-pharmacological package of care for knee pain. Where the nurse identified difficulties in delivering the intervention as intended, she was able to seek additional advice and trainingfrom MH. This experience has allowed us to further improve the nurse training programmefor use in the feasibility RCT by adding more complex case studies within the training manual.

Previous studies using mixed methods have explored factors that influenced fidelity and found good fidelity of delivery of a physiotherapist-led complex package of care for chroniclow-back pain and OA (Toomey et al., 2016, Toomey et al., 2017). They report on the factors that influenced fidelity on three levels: provider, participant and programme. Williams *et al* (Williams et al., 2020) demonstrated good fidelity of delivery of a walking intervention when delivered by nurses and healthcare assistants in primary care. Even though they used a mixed methods approach to assess fidelity, they did not integrate thefindings. In our study, the research nurse rated themselves higher than the independent rating using the video recordings consistent with previous studies. (Hardeman et al., 2008, Walton et al., 2020). Similar findings on barriers and facilitators to deliver the intervention have been identified in a complex intervention for people with dementia and chronic low back pain. (Toomey et al., 2017, Walton et al., 2020) In fact, Walton *et al* extended overthe factors that influenced fidelity of delivery (Walton et al., 2020) reported by Toomey et al. (2017) and recognised that knowledge, providers' attributes, ease of adaptation of the intervention in relation to participants' needs influenced fidelity. Based on the findings, itwas challenging to address adaptation and determine the appropriate balance between fidelity and adaptation in this study. This may indicate some key overlapping themes thatmay limit fidelity of delivery despite the different types of intervention and conditions.

There are a number of limitations to this study. A key caveat is that only one nurse was

involved in delivery of the intervention. In a larger trial, there would be more nurses to deliver the intervention across multiple sites, which increases the likelihood of variation infidelity. This study lasted 17 weeks and this is a short period of time over which fidelity may not fluctuate much. However, this can be an issue with longer studies (Radford et al.,2018). The nurse who delivered the intervention was interviewed but in the absence of data from additional participants, emerging categories could not be revised and refined into fully realised themes, however, an inductive approach to analysis was taken to reflectthe views of the intervention provider. A second interview with the nurse was conducted to capture any salient points not discussed during the first interview. We did not considerto capture engagement of the participants in the study. Complex interventions are often a dynamic interplay between patient and healthcare professionals. Whilst checklists can be helpful in determining whether an intervention has been delivered they do not allow foror capture the flexibility that is required when tailoring an intervention to the individual.

The intervention was delivered by a research nurse with no background knowledge of musculoskeletal diseases and no previous experience delivering treatment for arthritis. This is a particular strength as we were able to assess the effectiveness of our nurse training programme and its shortcomings. Additionally, we video-recorded and evaluated all the consultations that were delivered. One of the key strengths of our study was that we identified the specific components of the intervention not delivered as intended. Moreover, we triangulated the findings and found convergence providing internal validity.The nurse was interviewed to address some of the NIHBCC components (study design, provider training) that have not been examined previously (Toomey et al., 2017).

In conclusion, we found that nurse-led delivery of a complex package of care is feasible within a research setting. The research nurse-delivered care for patients with knee pain due to OA with high fidelity for most of the components of the intervention except for advice about the use of hot/cold treatments, walking aids, footwear, and goal setting. Webelieve that upskilling nurses to deliver complex non-pharmacological components for the

management of knee pain due to OA is feasible. Nurses would have more time to spend with patients and educate them about the condition. The training package for delivery of the intervention will need to ensure that the nurses are confident in delivering the behavioural change strategies such as goal setting. Follow-up training sessions and support during the start of the feasibility when nurses are first delivering the intervention may be helpful to improve confidence and delivery. Future work will need to consider fidelity where there will be more than one nurse delivering the intervention in a clinical setting where other factors will also influence fidelity. Our results, nevertheless, show that is feasible to apply the non-pharmacological package of care in a future feasibility RCT.

4.4.1 Key recommendations

Finally, we developed key recommendations to optimise the delivery and improve the fidelity of delivery of, and engagement with the non-pharmacological complex intervention. In terms of improving the fidelity of delivery, the first recommendation refersto the use of more case studies with more complex needs that should be added within thenurse's training programme. This is to ensure that the nurse is able to be flexible with participants who are not willing to lose weight and can adapt to individual patients' situations, which may affect their ability to implement the lifestyle changes. The second recommendation refers to boosted training sessions with the nurse and the training developer (MH) will take place as and when needed to instruct how to link the goal for the exercise with patients, as the nurse mentioned that they did not feel comfortable linking the exercise goal with patients.

5. Chapter-Acceptability of a non- pharmacological complex intervention for knee pain: Patient views and experiences

5.1 Introduction

Knee OA affects 16% of the general population worldwide (Cui et al., 2020) and its' management remains challenging in most healthcare systems due to the sheer disease burden and limits on resources. Patient education, exercise, and weight loss interventions for knee OA are often underutilised because of physicians' knowledge gaps, other demands on their time, and undue emphasis on drugs (Becker et al., 2017, Egerton et al., 2018, Egerton et al., 2017, Gignac et al., 2006, Nelson et al., 2014, Porcheret et al., 2007).

In the current model of care, patients with symptomatic knee OA may consult GP or hospital specialist and be referred to a physiotherapist and/or dietitian for exercise and weight-loss advice as appropriate. Whether nurses can be trained to effectively deliver a complex non-pharmacological intervention for knee OA that includes components that are traditionally delivered by other allied healthcare professionals is yet to be determined. This is likely to be possible as previous studies have demonstrated the efficacy of nurse-led care over usual GP-led care for chronic conditions when following a protocol, e.g., type II diabetes, heart failure, hypertension, and gout (Denver et al., 2003, Doherty et al., 2018,Driscoll et al., 2015, Fuller et al., 2019, Martínez-González et al., 2015, Sisk et al., 2006,Welch et al., 2010). Delivering care according to patient treatment preferences is of clinical importance and aids patient adherence, satisfaction with treatment, and outcome achievement. Interestingly, previous studies demonstrated that patient treatment preferences influenced process and outcome evaluation in RCTs (Mills et al., 2006, Rowe et al., 2005). Apart from this, it is not known whether nurse-led holistic care of knee OA would be acceptable to patients (as they would normally expect to be treated by different healthcare professionals for different aspects of their care) (Ayala and Elder, 2011). However, defining acceptability has been challenging throughout the literature, and inconsistency exists in theorizing the concept and providing specific guidelines on how to measure it.

In the UK, the MRC published three separate guidance documents (Campbell et al., 2000, Craig et al., 2008, Moore et al., 2015) for researchers to design and evaluate complex interventions and specifically highlighted the need to assess acceptability. Acceptability is determined by how well an intervention is received by the target population and to which extent a new intervention and its components meet the needs of that population (Ayala and Elder, 2011). Acceptability is also considered as any involvement in the study that will not cause harm to participants, their autonomy will be respected and the burdens of participating in the study will be outweighed by the benefits of research (Parry et al., 2016). Patients, therefore, are more likely to follow treatment recommendations if the intervention is acceptable (Fisher et al., 2006, Hommel et al., 2013). Previous research (Sekhon et al., 2017) developed guidelines to guide acceptability assessment in healthcare complex interventions. Acceptability isreferred to as a multi-component construct, which consists of seven key domains: affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs, and self-efficacy.

Methods to assess acceptability comprise self-report measures that refer to satisfaction measures, attitudes, interviews on users perceptions, experiences, and attitudes towards intervention, surveys, open-ended questions, interviews (barriers and facilitators of accessto intervention and support activities) (Sekhon et al., 2017). Behavioural assessments of acceptability are also suggested and comprise measures of observed behaviour such as drop-out rates, treatment discontinuation, attrition, adherence, non-compliance,willingness to participate/take test in future and withdrawal rates (Sekhon et al., 2017). The timing at which studies assess acceptability relative to the delivery of intervention is another factor they may need to be considered and pre-planned. Such assessments may be performed pre-intervention, during the intervention, or post-intervention. However, no study provided a threshold criterion for the intervention to be considered unacceptable. The purpose of conducting qualitative research in a complex intervention is to explore how an intervention has worked, and understand contextual factors that affect the delivery, especially if the

intervention includes a behavioural change theory (Michie et al., 2014). Therefore, understanding the context of an intervention is crucial to interpret and generalise the findings. The overall purpose of this study was to test the acceptability of a nurse-led non-pharmacological package of care for knee pain due to OA. The specific objectives were: to explore the experiences of participants who received the nurse-led non-pharmacological package of care for knee pain. The present study forms part of a wider programme of work (Hall et al., 2020) that aims to evaluate the feasibility of a large RCT for a nurse-led package of care for knee pain due to OA.

5.2 **Methods**

5.2.1 Study Design

Single-arm mixed-methods feasibility study including quantitative fidelity assessment which has been previously reported (Nomikos et al., 2021), and qualitative acceptability assessment which is reported here. In this study, participants were people with knee pain due to OA. For clarity, henceforth, we refer to them separately as 'patients'.

5.2.2 Reflexivity acknowledge statement:

The author (PAN) is a qualified physiotherapist registered with the Health and Care Professions Council (HCPC) and has previous experience treating patients with knee pain due to OA. This qualitative study is part of a doctor of philosophy degree conducted at the University of Nottingham under the supervision of two experienced qualitative researchers (AF, RdN). PAN conducted all interviews, was not known to the participants before undertaking this study, and did not undertake any local clinical activities alongside this research.

5.2.3 Recruitment

Eighteen people with knee pain who participated in the fidelity study (chapter 4), were approached by the research nurse at their final treatment session, and, the details of those willing to go ahead with an interview were passed onto PAN (Ph.D. student and physiotherapist). People with knee pain agreed to be interviewed after the end of their final treatment session.

5.2.4 Setting

This qualitative study was conducted in a private room in Academic Rheumatology, City Hospital, Nottingham where the fidelity study took place. Where participants were unable to attend the site, telephone interviews were conducted.

5.2.5 Ethical approval

Ethical approval was obtained for the feasibility cohort RCT and therefore it was deemed applicable for this nested research.

5.2.6 Consent

All participants gave written informed consent before the beginning of the study. This included optional consent for participating in the interview study.

5.2.7 Sample size

Theoretical saturation is the gold standard by which sample sizes are determined in qualitative research. Saturation takes place when no new information is observed in the data and is estimated to occur after the conduction of twelve interviews (Guest et al., 2006). Therefore, we aimed to recruit between 15 and 20 participants in the package development phase as this was expected to be sufficient to achieve data saturation. Additionally, given the risk of drop-outs and participants not attending for the interview visit, we aimed to recruit 15 to 20 participants in the study.

5.2.8 Patient and Public Involvement (PPI)

Three PPI members with hip or knee OA provided input into the content of the non-pharmacological treatment package and volunteered for nurse training. They have advised us that they would prefer the activity diary to be a tick box exercise rather than rating scale performance of 1-10. They have also informed us that the non-pharmacological intervention could be seen as a social activity from the participants so they could come in and socialise. Finally, they have advised us that spending 2-3 hours for the first visit would be too much and follow up sessions should be quick. For these reasons, the nurse advised patients filled the activity diary once a day as a "tick-box" exercise, and was advised not to spend much time with them during the first visit.

5.2.9 Data collection

People with knee pain who participated in the study and who received the intervention were invited to participate in a semi-structured interview. People with knee pain were interviewed immediately after the end of their final treatment session. Interviews were conducted using a narrative approach. Narratives are methods of knowing, presenting, and communicating personal experiences. Episodic knowledge and memory comprise two valuable aspects of the narrative approach, which are based on stories for knowing about issues, and remembering events (Metzler, 2014). Burden, ethicality, and intervention coherence are the key areas that represent the acceptability of the intervention.

5.2.10 Interview guides

A semi-structured interview guide for people with knee pain (Appendix VI and VII) was developed. Semi-structured interviews are the most widely used tools in qualitative research they are based on a schematic presentation of questions or topics that need to be explored by the interviewer (Jamshed, 2014). Interviews may occur either with an individual or with groups. However, individual interviews allow the interviewer to delve deeply into social or personal matters (DiCicco- Bloom and Crabtree, 2006). The topic guide's questions comprise the core question and many associated questions related to the central questions may improve further with pilottesting of the interview guide (Jamshed, 2014). For this reason, pilot interviews with admin staff members from the University of Nottingham took place to test and refine the interview guide. AF provided feedback and PAN amended the interview guide accordingly adding prompts/probes. The interview guide was still improving after each interview withthe participant, as this was an ongoing process where the researcher engaged in an in- depth description and became more familiar with the interview guide and the participants.

This data collection method was preferred as it allows the interviewer to explore views ofthe interviewees comprehensively and systematically and provides with the opportunity toalter the questions as the interviewer learns more about the participants (DiCicco-Bloom and Crabtree, 2006). The interview guides contained open-ended questions and were developed by the study team, which included a rheumatologist (AA), physiotherapists (MH, PAN), psychologist (RdN), and qualitative researcher (AF). The interview guide for people with knee pain covered: perceptions of disease management before, during, and after thenurse-led intervention; changes in perceptions of knee pain after the study; their experience of the intervention, the provider and delivery of the intervention; lifestyle changes; and, overall satisfaction with the treatment.

Before starting the interview, it was explained that the participants' responses would remain confidential and that any quotes included in future publications would not identify them. Participants were informed of the right to withdraw from the interview at any time. All interviews were conducted in a private room in Academic Rheumatology, City Hospital, Nottingham. Where participants were unable to attend the site, telephone interviews were conducted. PAN conducted the interviews and was trained in conducting one-to-one semi-structured interviews by an experienced qualitative methods researcher (AF). AF was present during four interviews. During the first interview, AF was the research facilitator and led the conversation with PAN supporting. In the following three interviews, PAN led the conversation with AF supporting.

5.2.11 Data analysis

A theoretical framework for assessing treatment acceptability has been published (Sekhonet al., 2017) and guided the evaluation of acceptability in this study, with burden, ethicality, and intervention coherence being the key areas that represent the acceptability of an intervention. The theoretical framework was adapted from those published in previous literature (Sekhon et al., 2017).

Data were analysed using the framework approach (Gale et al., 2013). The framework method is becoming increasingly popular in health research (Gale et al., 2013) and allowsthe researcher to analyse data during the collection process (Spencer and Ritchie, 2002, Ritchie et al., 2013, Pope et al., 2000). This method (Spencer and Ritchie, 2002), sits within the broad family of thematic analysis techniques as it has many similarities with thematic analysis, especially in the initial stages when recurring themes are identified (Smith and Firth, 2011). In addition, the framework method makes the data analysis process more transparent and shows the linkage between the stages of analysis. It was used in this study as it has clear steps to follow, it compares and contrasts the data, andcan be used by less experienced qualitative researchers in a multidisciplinary team (Gale et al., 2013) always with the leadership of experienced qualitative researcher (AF). All interviews were audio-recorded and transcribed verbatim by an external transcription

company. Following this, transcripts were imported to NVivo 12 for analysis. Transcripts were reviewed and checked for accuracy, and any personal identification removed. Transcripts were read several times by PAN and segments of text coded. AF read a sampleof three patient interviews and independently coded the transcripts. PAN and AF discussedinitial codes, themes and sub-themes, which resulted in a working analytical framework. Codes identified in the nurse interview and patient interviews were similar and thus thesewere analysed together. The framework was then applied and refined following analysis ofthe remaining transcripts by PAN, and through discussion with the wider research team. Data were then indexed according to the final analytical framework (Table 5—1) and charted according to each theme, which facilitated data synthesis and interpretation. Mean and SD, n (%) were used for descriptive purposes.

Table 5—1 Coding framework (Themes and corresponding themes)

THEME NAME • Sub-theme name
PREVIOUS TREATMENT EXPERIENCES
• Care provided by previous healthcare practitioners
• Previous healthcare practitioners attitude towards participants
• Concerns for the benefits or side effects of previous treatments received
• Barriers to continue following the weight loss advice and carry out the exercise in previous treatments
PARTICIPANTS PERCEPTIONS FOR THE PACKAGE OF CARE
The overall perception of the package
• Participants perceptions of the nurse delivering the package ➢ Nurses ability to treat knee pain ➢ Nurse's attitude delivering the package ➢ Nurse's barriers to delivering the package
• Perception of weight-loss strategies
• Perception of the exercises
• Perception around the Arthritis UK booklet
• Perception of adjunctive treatments
RAISED AWARENESS ON THE SELF-MANAGEMENT OF KNEE PAIN
• Knowledge before the intervention ➢ Perception of OA before the intervention
• Knowledge generation ➢ Illness perception addressed
• Knowledge reinforcement ➢ OA perception reinforced
• Impact of new knowledge ➢ Changing behavior
ADHERENCE OF THE PARTICIPANTS TO THE INTERVENTION
Adherence to the advice in the development phase
• Individual psychological factors
• Disease-specific factors
• Trial participation
• Members involved in the knee pain management
• Accountability to the nurse through the use of follow-up sessions
Perceived ability to continue and follow the advice of the development phase
➢ Barriers to continue and follow the advice of the development phase
KNEE PAIN AND QUALITY OF LIFE BEFORE AND AFTER THE STUDY
• Impact of knee pain on the participants' basic activities of daily living
• Impact of knee pain on the participants' sports and activities
• Impact of knee pain on the participants' mood
• Impact of knee pain on the participants' sleep
• Impact of knee pain on the participants' social activities

5.3 **Results**

Eighteen white British adults with chronic knee pain took part in the study. Their mean (SD) age was 68.7 (9.0) years, 34% were women and the mean body mass index (BMI) was 31.2 (8.4) kg/m^2. Participants' demographics and characteristics are collected and presented in Table 5—2.

Table 5—2 Participants' demographics and characteristics

ID	Age (years)	Gender	Weight (kg)	Height (cm)	BMI
KPS0077	60	Male	105.9	169.3	36.9
KPS0043	65	Female	79.9	178.7	25
KPS0026	82	Male	89	171.5	30.2
KPS0116	87	Female	87.8	157.4	35.4
KPS0010	63	Female	72	167.5	25.6
KPS0114	64	Male	169.2	174.8	55.3
KPS0020	66	Male	153.3	181	46.7
KPS0063	54	Male	93.2	169.5	32.4
KPS0076	63	Male	79.7	181.5	24.1
KPS0069	78	Female	73.2	159.5	28.7
KPS0049	84	Male	103.7	168.5	36.5
KPS0071	57	Female	80.5	171	27.5
KPS0099	74	Female	71.2	157	28.8
KPS0054	65	Male	88.5	178.8	28
KPS0080	74	Male	75.5	168.2	26.6
KPS0023	65	Male	79.8	176.3	25.6
KPS0117	65	Male	78.1	176	25.2
KPS0033	71	Male	66.9	167.5	23.8

Based on their BMI, nine were categorised as overweight and seven obese. Seventeen out of eighteen were interviewed including three of the four who did not attend all treatment visits. One participant was not contactable after the baseline visit and dropped out of the study. This participant did not participate in the interview. Participants, who did not attend all treatment visits were mostly females (75%) with mean (SD) age 64.8 (6) years and a

lower BMI 27.5 (1) kg/m^2 compared with those who completed all visits. All non-attendees had moderate knee pain severity (Table 5-3).

Table 5—3 Demographic details of participants according to whether they attended or did not attend all treatment visits

Participant demographics	**Attenders (N=14)**	**Non-attenders (N=4)**
✞ Age (years)	69.8 (9)	64.8 (6)
✞ BMI (kg/m2)	32.3 (9)	27.5 (1)
Females (%)	21	75
Retired (%)	86	100
Knee pain severity (%)		
Mild	36	-
Moderate	29	100
Severe	35	-

✞ Values shown are mean (SD)

Of those who dropped out of the study (n=4), one took part in a telephone interview. The nurse had no previous specialist knowledge of musculoskeletal diseases and had never delivered treatments to arthritis patients before. The average length of the interviews was 54.8 minutes (range 25-84 minutes). Five main themes were identified from the analysis of the interview data:

1) Previous treatment experiences

2) Participants perceptions for the package of care;

3) Raised awareness on the self-management of knee pain;

4) Adherence of the participants to the intervention;

5) Knee pain and quality of life before and after the study;

5.3.1 Previous treatment experiences

The first theme of five covers the participants' perceptions and experiences of previous visits to the doctor, referrals and their communication with the healthcare practitioner in relation to their knee pain.

Care provided by previous healthcare practitioners

Most patients who had seen their GP for knee pain had been prescribed painkillers. General care that was provided consisted of minimal invasive surgical operations such as arthroscopies, steroid injections, painkillers, ibuprofen gels and referrals to secondary care. Some of the patients were referred to a physiotherapist after they had a knee arthroscopy, who prescribed them with exercises. *"I had the first arthroscopy, on my first knee, it didn't get better very quickly and I was referred to a physio then, and given physio exercises" (KPS0010).* For those who had the knee arthroscopies, the doctor also offered them the option of total knee replacement later on.

Previous healthcare practitioners' attitude towards patients

Some patients felt that their GP and/or physiotherapists were apathetic towards them. *"You get a session with a doctor, but it's not life threatening, so they're, to be honest not really that bothered" (KPS0033). "The doctor never seems to have enough time to tell me anything about anything" (KPS0117). "They don't seem to be interested, I think that's why, and … rightly or wrongly, I've probably got this thing in my head that they're not gonna do anything till I can't walk" (KPS0023).* For some patients, the GP did not attempt a diagnosis with an x-ray and relied only on the clinical presentation of OA. "*They never sent me for an x-ray, after the injection didn't work, I was sort of, you know, mentioned my knee pain, "its age, you know, we can't do anything about it"" (KPS0026).* For one patient, their GP was unable to provide any more advice/information on how exercise can help and then that patient visited a physiotherapist. *"I suggested that I would do some exercises and he [doctor] said … "try it and see what happens" (KPS0117).* For those who have seen the physiotherapist it was a very short session and they felt there was not enough time to fully understand how to do the prescribed exercises properly, and the

purpose of them. *"I didn't understand what it was I was doing, because it was such an intense short period, only go and see her for half an hour so it was "do these exercises and go", I never really understood why I was doing it" (KPS0117).*

Concerns for the benefits or side effects of previous treatments

All patients who had a knee arthroscopy reported that their knees did not heal up very quickly. Most were concerned about taking paracetamol for a long period. One patient thought that masking the pain by taking paracetamol might cause more damage to the joint as they might overdo activities that would not normally do when having knee pain, *"I have a mental attitude to the point that it's … masking pain … can you mask it that much? You're going to overdo it, you think "oh I feel fine" and then you just carry on use-when you should have rested or whatever and that" (KPS0080).* One patient reported that codeine and tramadol had had detrimental effects on their kidneys and they swapped to paracetamol instead. Other side-effects patients reported from capsaicin, turmeric, paracetamol, and diclofenac were eczema and stomach upset. Diclofenac had long-term side effects but worked better than paracetamol (in terms of easing the pain). Some patients perceived that paracetamol and ibuprofen tablets do not work. Voltarol gel seemed to work better than ibuprofen gel for one patient but they could not tell if they could see an effect.

Barriers to continue following the advice/exercise in previous treatments

The majority of the patients reported that they did not follow the advice on the exercise provided by healthcare professionals in the past. The most common reason for this was the lack of detail in the explanation for the treatment provided by the previous healthcare practitioner: *"I never really understood why I was doing it and I just … I just dropped the exercises off then because I didn't know why I was doing it" (KPS0117).* Some felt that the exercise advice provided was complex and unclear, which also resulted in them not understanding the role of the prescribed exercise. In contrast, for others lack of motivation, lack of monitoring by the healthcare provider, lack of interest were other key reasons why they did not follow healthcare professionals advice: *"I received with some exercises, but again I'm probably like lots of other people, you do them, and then you*

don't do them" (KPS0043). Two patients discontinued with the advice from their doctor and stopped taking tablets (painkillers and diclofenac) due to the detrimental effect on their kidneys.

5.3.2 Participants' perceptions for the package of care

The second theme covers the participants' perceptions for the format, content and delivery of the intervention. Its treatment regime and principles and how patients achieved their goals.

Overall perception of the package

Most patients were satisfied and pleased with the package but felt that too much information was provided too soon. *"It's been very beneficial, very good" (KPS0020). "Very good. That is all I can say really" (KPS0023). "I think you know, if you were looking at the study from my point of view, I would think it was perhaps a little bit too much too soon" (KPS0049).* According to one patient who discontinued with the study, and was not satisfied with the package, the nurse should have focused more on the exercise rather than anything else, as the other components of the package were common knowledge. *"I would say then it's got to be down to the exercising, it's got to be because everything else that she was talking about was what I think is common knowledge!" (KPS0099).* A few of the patients reported many demands from the nurse starting from the first week. According to one patient, there was a lack of detail/explanation during the consent process, and they had not realised the extent of involvement required by patients in the study. *"When I signed on, obviously they didn't go into as much detail as they did when Istarted the study, so I didn't know what to expect"(KPS0054).* The nurse stated that one patient didn't recall reading the information provided during the recruitment process. Patients felt that the intervention overall was a complex informative package but the majority, and the nurse delivering the treatment, felt that the first session could be divided into two or three, because it was too much information the first week. *"I think the person who is … doing the exercise programme, I think the, these sessions could be divided in different ways so first session, you just get to know the patient and they get their feedback and, don't give them any, too much of a diet and weight loss information" (KPS0001).*

Patients' perception of delivering the package

Patients' satisfaction with the nurse's actions

Nurse's ability to treat knee pain

Patients appreciated that the nurse provided the opportunity to talk which they did not getwith the GPs/physios. "It's the first time that I've actually had the time to talk about themwithout feeling that I've got to get in and out of a room" (KPS0117). Most patients perceived that the nurse used lay language, explained, demonstrated and corrected theirexercises. Patients stated that the nurse was a good listener and good communicator, very attentive, knowledgeable, and felt they were suited to deliver this type of treatment. Thenurse reported having low confidence in her ability to deliver the treatment in the beginning, as a result she chose to prescribe all exercises for the patients in the first instance. Then she felt more comfortable. "I don't know, I don't think after a few sessionI was uncomfortable, I was probably more comfortable delivering the, I wouldn't say I was very confident" (KPS0001). Patients also stated that the nurse appeared to be more comfortable as the sessions went on. The nurse did not feel comfortable with the goal setting and stated that she let the patients decide and set their own goal.

Nurse's attitude to deliver the package

The majority of the patients agreed the nurse was approachable and friendly. Most patients stated that the nurse built rapport, which created a trustworthy therapeutic relationship. However, one patient felt the nurse was very firm when discussing how to fit the treatment regime into patient's daily routine. That patient had other commitments throughout the day. *"She said, "When are you going to do the exercises?" I said, "Well in my time, whenI can fit in me…" "No…you can't do that! You have to do it at a set time in the day, it's the wrong attitude and I've done staff jobs" (KPS0099).* Two patients stated that the nursewas quite rigid on setting time aside for the treatment regime. *"She's very much keen onthe idea that you should set aside, you should say, "This is your exercise time" and you go all the way through everything" (KPS0116).*

Perception of weight loss strategies

Most patients were satisfied with the weight loss advice. Measuring calorie content on foods made the patients realise how much they were eating and cut down on specific high calorie foods. Many patients acknowledged that reading food labels was challenging but very important for them to realise what they were consuming. One patient did not find the weight loss advice useful and argued that the calorie websites they were referred to by the nurse did not correspond to the food labels, and therefore their recorded calorie consumption was not accurate.

Despite the fact that their BMI was above 25, many patients felt that their weight was normal and they were not happy to receive advice about losing weight. One patient did not follow the weight loss advice because they felt they should not cut down on food at that age. *"No ,there's no way, no way. I like my food and I've seen so many contemporaries go off food and it's the beginning of the end, when you go off your food at my age" (KPS0049).* Two of the patients felt aggrieved when the nurse advised them to lose weight. One patient had already lost some weight before entering the study. *"There was no kind of need to explain to me that I need to lose weight, well I was a bit annoyed because I've lost half a stone". "When she said about losing this weight I'm thinking, "She thinks I'm fat" (KPS0099).* One patient who dropped out was concerned about following a lower calorie diet because he wasn't prepared to lose weight and did not like that the nurse will be measuring his weight on each visit. *"I wasn't ready to do that…she said, I'll weigh you every time you come, you see, I knew because I wasn't sticking to any diet, I wasn't going to lose any weight" (KPS0054).*

Perception of the exercises

Many patients felt that the nurse prescribed too many exercises on their first session, which caused physical discomfort. *"There was a little bit of physical discomfort doing the exercises" (KPS0054).* Although most found the exercises were painful and tiring in the beginning, as they continued to do them daily their pain became less frequent and less intense *"A couple of the exercises that I had to begin with …were quite painful to be*

honest…the pain is getting easier, less frequent, less intense" (KPS0023). However, they also found the exercises took about one-hour to complete each day, which many felt was very time consuming. *"when I was working, I was already getting up at like 6 o clock, to get up at 5 o clock, to have done an exercise regime, I would have found that really, really difficult so for me*" (KPS0023). *"It's taking me 50 minutes to do my exercise every day, well that's a long time to be doing it if I'm doing it every day for the rest of my life" (KPS0117).* Most patients acknowledged that the exercise sheets aided performing the exercises at home, as they served as a reminder of what the nurse had demonstrated to them during the research sessions. However, the lack of description within the exercise sheets made some patients feel uncertain on how to perform the exercises at home. They felt that the exercise sheets could have had more detail, such as a more in-depth explanation and instruction of the body position and which leg to stretch/strengthen. The nurse also felt that the exercises sheets could have been more descriptive. Some patients suggested adding numbers to help identify exercises to perform. *"If you could have identified the exercises like say perhaps with a number or a letter" (KPS0116).*

Perception around the Arthritis UK booklet

Many patients felt that the booklet did not provide any additional knowledge above or beyond the nurse's advice provided during the research visits. Rather, it worked as a complementary element for the intervention reinforcing information about OA that they already knew and acting as a reminder for the exercises they needed to do. *"I think they complemented each other, so… there was nothing in the booklet that we didn't talk about" (KPS0076)*, *"I did read it, and it reinforced things I already knew" (KPS0063) "The book was essential, as far as me remembering the exercises and what she said about the exercises and that the basic ex- exercises in the book" (KPS0026).*

Perception of adjunctive treatments

Some patients were using their walking sticks prior to the study to increase their confidence in walking. *"I was using the stick for so long, that I needed it for that reassurance" (KPS0020).* Most patients either did not receive advice on adjunctive

treatments from the nurse or could not recall whether the nurse covered them during the study *"I don't think we covered that" (KPS0033), "I think she did mention that" (KPS0043)," No, didn't cover those, no"(KPS0049), "I wasn't advised" (KPS0063), "No, not sticks…no…no" (KPS0099).*

5.3.3 Raised awareness on the self-management of knee pain

The third theme covers the patients' new knowledge as a result of the intervention

Knowledge before the intervention

Most patients perceived OA as a condition that would get worse with aging with no treatment available and the only option for improvement would be total knee replacement surgery. *"I didn't know, that simply doing the exercises would improve, I would have thought the only solution would be an operation so that's what I've learned, or one of ththings I've learned" (KPS0026).* Most patients were resigned to the idea that their OA would continue to get worse. *"I was kind of…resigned to it getting worse" (KPS0076)*. A couple of patients were already aware of the benefits of exercise and weight loss on reducing knee pain. *"The knowledge actually is … I knew that obviously you didn't want, your weight is the problem, you carry more weight, you've got more wear problems and that, and so I was fully aware of that" (KPS0080).*

Knowledge generation

As a result of the intervention, most patients' reported gaining new knowledge about food calorie contents which made them realise whether they were eating healthily or not. *"You want to read the labels because there's a lot of fat and a lot of salt in them, there really is. For something that's such a small portion, there's a lot of fat and a lot of salt in them, and I didn't realise that, because I wasn't looking" (KPS0020).* Patients also learnt about the importance of getting out of breath during their activities of daily living (e.g. walking) or during any sort of exercise and increase their heart rate to achieve some aerobic activity. *"That's something again I've learned from being here, that I've got to push myself more to get my heart rate up" (KPS0043).* Some patients became aware of the importance of building muscle around the knee joint and losing weight, which would help them alleviate

their pain and improve their condition. *"I didn't know exercises would help before,no, I thought it was worn out! And you know, but, the muscles they've gone and that wasit but… then I was told that they could, you know, by exercises, be strengthened and improved" (KPS0049).*

Knowledge reinforcement

Some patients were already aware of the benefits of exercise and weight loss in helping them to manage their knee pain. *"It is stuff that I probably knew anyway, weight bearing on it has an impact, not exercising or not trying to exercise it has a negative impact" (KPS0063).* For those patients, the package worked as a good reminder and reinforced the knowledge of diet and exercise for OA rather than providing new knowledge. *"This has served as a reminder as opposed to teaching me anything if you like". "I suppose she's reinforced what I already thought about exercise and diet; she's just reinforced it for me" (KPS0023). "It was good to go over some stuff again" (KPS0063).*

Impact of new knowledge

Most patients reported that the package changed their perception of managing their knee pain, understanding that it can be improved through self-management. *"I say, the whole thing if nothing else, it's focused me and made me reset and try again and think perhaps it could be better than it is. Rather than thinking this is it, it will only just get worse" (KPS0063). "This package it's kind of changed my attitude really and if I can improve things muscle wise and mobility wise, then things could get better" (KPS0076).* The package increased patients' motivation to perform the exercises and achieve weight loss. "*I feel better in myself… pushing myself even when it is a bit uncomfortable" (KPS0063). "I am not fit, but I am active, but I don't push myself and I realise that I need to push myself". "I have been pushing myself too, even cutting down on my cider" (KPS0043).* Some patients reduced their alcohol intake. *"I drink beer a lot, I drink wine like I drink beer, you know, so it's one of those things that ... So it's not only helped the dietary side of it, it's helped cut down on the alcohol as well" (KPS0114).* Others started reading food labels and measuring their portion sizes because of the information learnt. *"The biggest*

impact I've found is when she got me to read the labels, because I never used to read labels" (KPS0020). Patients are hopeful their knee pain will improve if they implement the advice given. *"I'm thinking I may be able to keep it as it is not worse, I may be able to improve it slightly…which again would be, would be a bonus" (KPS0063).*

5.3.4 Adherence of the patients to the intervention

The fourth theme covers patients' adherence to the advice

Adherence to the advice in the development phase

Some patients stated that they found it easy to follow the advice by the nurse. *"Easy, yeah, I found it easy to follow, the things we talked about and yeah, it was fine" (KPS0010).* Others find it more challenging especially at the beginning. *"Well it was a little difficult at first; I don't think I would find it easy, counting calories" (KPS0069). "I think the basic problem we may have is that first week, getting your life routines to fit this in such as all the other people have the same problem" (KPS0080).* A few patients found it difficult counting calories. *"I wasn't prepared to calculate as I went along all of the, you know, the calories in each item of food, I thought Oh I can't do that" because it's such a difficult job" (KPS0026).* Those who were able to find time aside and establish a routine to perform the exercises were able to adhere to the advice given by the nurse*. "I had to have a specific time, because I, I do what I want to do in the mornings" (KPS0043). "I've sort of more or less developed a schedule to do these things… it has become part of my routine" (KPS0049).* However, some patients found it challenging to find time aside for the exercise regime. *"Basic problem we may have is… getting your life routines to fit this" (KPS0080).* Some patients also stated that adding more and more exercises in their regime can be time consuming and will make them feel bored. *"To add on and add on, it's time consuming and, and that, I think that can make you …get bored, so I'm quite happy where it is really" (KPS0069). "If I start adding more exercises in that she's [Nurse] given me this morning, an increasing number of repetitions, it will take longer and I think that will be … the thing that will, that will play on my mind" (KPS0023).*

A couple of patients had difficulties setting time aside as they did not have a specific timeframe/routine to do the exercises. *"I was always thinking about, "I've got to do the exercises", when, "when is the best time to do it?", because after a meal, it might, it could, could have given me indigestion so I've got to let an hour, at least an hour after a meal and then … you've got your normal living activities" (KPS0026).* Patients who were already exercising combined the exercise regimeinto their gym routine and performed the knee-targeted exercises at the gym. *"Iincorporated some of those exercises while I was at the gym" (KPS0010).* One patient who dropped out of the intervention after two sessions found it very difficult to keep up with astrict exercise and diet regime and did not believe the exercises would lead to an improvement in their knee pain. As a result, he did not want to set any time aside to perform the prescribed exercises, preferring instead to do his own exercise regime. *"I'm doing it in my own way, but not as intense as what the nurse wanted me to do… I've got a thing about physiotherapy, I don't really know whether it, whether it works or not" (KPS0054).*

Members involved in the knee pain management

Another factor that aided adherence to the exercise and/or weight loss for some of the patients was involving partners or friends. During patients' home exercise performance, family members helped them setting up some equipment for some of their exercises (Thera-bands) or assisted with the exercise counting (reps and sets). Equally, family members were involved in the weight loss regime, by printing out sheets with calorie information for their food products and encouraging the patients to follow the weight loss programme. Others involved neighbours with knee pain who had previously participated in research programmes and compared notes with them. *"I was just walking by…the garden… and he [Neighbour] says I've been away on a course… it's to do with arthritis of the knee… [Neighbour's name] was saying that his knee movements and so forth are sort of more limited, so I said, Well I'm on this so … I'll copy you my exercises and you have a go and see how you get on and every now and again we'll compare notes and, and see*

how we are and support each other" (KPS0116).

Individual psychological factors

Commitment and self-discipline to perform the exercises and follow the weight loss advice in the belief that these would improve their knee pain also drove several patients to adhere to the advice. *"This is something that is easily relatable to, and you can go back to and you know, with the numbers of reps and everything, it's a good discipline" (KPS0076).* Filling the food diaries to achieve their goals was a good discipline and made the patientsfollow the programme as they stated *"It was, me knowing about calories, writing down what I'd been eating, and so on" (KPS0043). "I fill in my folder ... just after I've eaten mybreakfast, about everything that went on the day before, I'll make sure it's complete for the day before, so that was a very good discipline" (KPS0117).* As one patient explained,this made them feel committed to making those changes *"It's no use just ticking the boxesand pretending that doesn't help anybody, if you want to make an improvement then you've got to, you've got to do it, you've got to be committed to it". (KPS0076).* Patient motivation and willingness to change influenced adherence.

Disease specific factors

One patient reported he was not motivated to follow all of the advice because his knee pain was only mild, and had his pain had been greater he would have been more motivated to do so. *"I mean thatwould have been a good, better motivation to carry on, had it been excruciating" (KPS0054).* The same patient perceived the intervention as a complete lifestyle change and stated that this was not worth what he would get back. *"You know, you've got to be motivated and like I say it was, it was a payoff between my level of pain, and the amountthat I had to do to off balance it" (KPS0054).*

Trial participation

Other patients with low-level knee pain, who did follow the advice of the study, reported

doing so because they wanted to help with the research programme. *"It was the participation, because if I'm doing it for myself, before I came here, I was quite happy with myself. You know what I mean, I didn't, I was managing, and I wasn't a major problem in my life, because I accepted the pain" (KPS0043). "I wanted to put in as much as I could to that so I not, not so much, it was just as much about me wanting to do something for me as it was to help you do something for you, so I probably had a dual focus" (KPS0117).* However, one patient that dropped out was worried that his compliance in the study will not be satisfactory, as he felt accountable to the nurse in a negative way. *"I didn't really want to let her down, you know, I thought well you can get somebody else who's going to be more compliant, you're going to get a better result, you know" (KPS0054).*

Accountability to the nurse

Having someone to be accountable to also drove several patients to adhere to the advice provided. As the nurse was measuring their weight and checking on their exercise progress during the weekly follow-up treatment sessions, many patients followed the programme as they felt accountable to her*. "Somebody was going to be measuring it and somebody was going to be saying, "You've lost this much" or "You've stayed the same" or "You've put some on" (KPS0023).*

Barriers to continue and follow the advice of the development phase

Others reported that social events, activities, ready meals, holidays and birthdays would be the barriers to continue and pursue with the dietary advice. *"During this last month or so, you know, there's been a wedding to go to, there's been a spa day to go. There's been activities, birthdays" (KPS0043). "Getting over this holiday barrier has been a good one for me as well. I'm not saying there won't be any hiccups on the way, there will be" (KPS0114). "I would have found following the dietary advice easy but it wasn't easy because it was unusual that my birthday fell in the middle of it" (KPS0116).*

Perceived ability to continue following the advice of the package development phase

Even though patients were quite confident and motivated to continue and follow the advice from programme, they had felt very accountable to the nurse to follow the exercise and weight loss advice and would have liked to another session, at a later date, for the nurse to follow their progress. *"A follow up in say three months, it's helpful, you know, I am okay to be motivated by myself, but to know that you would know that, you know, that it continued, I just think that would be quite nice" (KPS0043).* Having built a routine to follow to do the exercises over the four-week programme, some patients' felt they could continue to follow the advice in the long term. Those whose family members involved themselves in the programme and started exercising with them, then felt accountable to them*: " I f-feel a bit responsible to her [patients' wife] as well, if I stop doing it, she'd stop doing it and doing exercise as well, my exercises, yeah, so I feel accountable to my wife" (KPS0026).*

Others reported that they would continue to use the diaries to help them carry on following the advice, and gradually increase the reps of the exercises. *"I've got some diaries to carry on filling in and I will tweak the exercises slightly, increase the reps or whatever else, or the loading" (KPS0033).* Having noticed the benefits of the programme on mobility and weight loss, many patients' felt quite confident that they will continue.

Implications for continuity of care

Certain elements in relational continuity that refers to attitude, confidence (from the healthcare practitioner), good communication and good rapport may make patients adhere better to treatment recommendations more, leading to improved outcomes. We have shown that poor communication and time management skills from the previous healthcare professional are sources of dissatisfaction in primary care that led patients to stop following the advice from the previous healthcare practitioner (as shown in 5.3.1). Demographic and personal psychological characteristics may also influence the continuity of care as well as providing complete information regarding their needs about the condition and the different available treatment options in which they can fully understand.

5.3.5 Knee pain and quality of life before and after the study

The fifth theme covers the effect of knee pain on the patients' activities of daily living, mood, mental health, sleep, personal relationships, employment status before and after the package development phase.

Impact of knee pain on the patients' basic activities of daily living

Knee pain caused limitations on all the patients' usual activities of daily living. Some patients found simple activities problematic such as prolonged periods of standing and getting up from a low chair. *"Because obviously on site you're, people standing talking and you're got to try and sit down some time" (KPS0077).* Using public transportation was difficult and most patients experienced knee pain during walking and had a permanent limp. *"It was causing me pain when I was walking and when I went down stairs it was like a constant tooth ache" (KPS0099). "I have to watch what I do. Going on public transport, buses… I try not to do that because if I get jolted that could put me in a wheelchair" (KPS0099).* For some patients, walking got quite slow and many relied on a walking stick as they had experienced frequent falls so were not confident enough to get around without one. When climbing stairs, they also needed to hold onto a handrail or wall for reassurance. For most patients, going down stairs and slopes was worse and more painful; *"I've found its worse coming down the stairs than what it was going up" (KPS0026). "I'll be honest with you; I used to think, because going down a slope is bad for me. If I'm in a slope walking downwards, that's a nightmare" (KPS0114).* Those who were overweight found it harder going upstairs, and often their legs gave way whilst doing so. *"Going up the stairs I'm having to push me weight up, which is obviously what the problem is, and I've got very little confidence in me left knee" (KPS0114).* Extra weight also had an impact on the patients' walking in general. Some patients mentioned a catching sensation of their knees after and when using the staircase. Activities that required kneeling on a flat surface such as gardening were painful and made their knee more swollen for everyone. Activities such as getting in and out of a car and getting in and out of the bath required assistance. The cold weather affected the joint and made it stiffer. After the end of the study, for most

patients their walking ability was improved, as they are now walking faster, and they have stopped, relying on their walking stick (mentioned that they are now more confident). They have noticed an improvement going up and down the stairs and have stopped holding the rails. *"I'm certainly walking better" (KPS0020). "The stairs aren't too bad, since I've been doing these exercises" (KPS0023).* However, one patient stated that walking, climbing stairs now is more difficult, and he started relying on his walking stick again. *"Climbing the stairs, going down the stairs of course is, has got more difficult. I always take my walking stick now, whereas up to two weeks ago, I didn't" (KPS0026).* In particular, that patient found it difficult to adhere to the programme.

Impact of knee pain on the patients' sports and activities

Most patients had physical limitations due to their knee pain on sports and activities. In fact, some have stopped attending their gym classes as the exercises became painful, and all who had played sports such as tennis or football had stopped due to their knee pain. Even non-weight bearing activities such as swimming had become more difficult for some patients. *"f-for a long time I-I swam a lot and I would play badminton…but now that's, that's really out because my mobility is just so poor… you know, I don't, I don't really bother" (KPS0076).* At the end of the intervention, some patients felt that they were able to do gym exercises more easily. *"At the gym, there's a treadmill, and there's a cross trainer, which I never, ever used to use, well again I now do, and I can manage you know, 10 minutes or so on the yeah on the treadmill"(KPS0043).*

Impact of knee pain on the patients' mood

Before the study, some patients stated that limitations in mobility due to knee pain caused frustration got them down, and they were not feeling so good. *"Getting out of bed, maybe walking about a bit and not being as lithe as I used to be has probably affected my mood" (KPS0054).* Few patients reported that following the advice influenced their mood in a good way and made them feel a lot happier because they were not getting out of breath as they used to. *"I feel a lot, lot better in myself. I don't get out of breath so much, I'm not wheezing as much as I used to do" (KPS0020).*

Impact of knee pain on the patients' social life

Knee pain previously had a negative impact on the patients' social life, finding it difficult to engage with friends and not being able to actively participate in social group activities. *"I've got a circle of friends that understand that, so they wouldn't ask me to go and play rugby with them or things like that" (KPS0063).* Other social engagements such as attending the church, and family and neighbour gatherings were also quite difficult for many. *"I can't go out with a group of friends, if they're going to say a fair or a market or something like that" (KPS0114).* However, the intervention improved patients' social activity (walking with friends). *"If you're out with people and they're all walking at a certain pace, you tend to find you're lagging behind a bit, even though you're going as quickly as you can… I'm not going to be any Olympic running or anything but I have noticed it improving" (KPS0063).*

5.4 Discussion

This study assessed the acceptability of a non-pharmacological package of care for knee pain by exploring nurse's and participants' views and experiences of delivering and receiving the treatment. In this study, a trained research nurse was the sole contact with participants and managed the core non-pharmacological treatments independently. We assessed both post-intervention (retrospective) and anticipated (prospective) acceptability based on their views and experiences of what it would be like to continue with the intervention as part of an ongoing routine care. The study followed guidelines for acceptability assessment (Sekhon et al., 2017) and assessed acceptability across intervention coherence and burden.

Intervention coherence refers to the extent to which participants understand the intervention and how it works. In the present study, most participants understood the commitments they would be required to make and acknowledged how the intervention might work: via exercise, weight loss, and a better understanding of the disease process. Not unexpectedly, most people with knee pain stated that the most challenging part of the

intervention was to fit the exercise regime into their daily routine.

The intervention burden reflects the reasons for discontinuing the study and the perceived amount of effort that is required to participate. Although the overall trial recruitment (from which this study sample was drawn) was small (n=18), only four participants did not attend all treatment visits. Two people who left the study stated that they were not able to make the required lifestyle changes or find time for doing the exercises at home

For such complex interventions to be effective, the use of strategies to motivate patients and support adherence to healthy behaviours are also required (Michie et al., 2011, Michie et al., 2014). The nurse was able to implement them for the majority. The treatment package changed patients' perception of managing knee pain by improving their understanding of the nature of OA and the rationale behind the use of non-pharmacological interventions and its management. This was done by individualised discussion on the nature of OA, risk factors for its onset and progression, mechanism of action of non-pharmacologic interventions, and the fact that OA symptoms improve with exercise and/or weight loss in the short-term and potentially also in the long-term.

Overall, the vast majority of knee pain people attended all treatment visits. However, the people with knee pain that did not attend treatment visits were younger, mostly female, and had lower BMI. Given the small sample size firm inferences cannot be drawn from this observation and this finding should be explored further in the pilot RCT.

Key action points on how to modify and optimise the package of care in preparation for the feasibility RCT were identified. These include building in greater flexibility in the treatment package according to the individual needs of the patients, i.e., greater emphasis on exercises for some while a greater emphasis on dietary and lifestyle changes for others,and further nurse training on goal setting and linking the goal to the exercises prescribed.Some participants found it difficult to practice exercise with the exercise sheets. We will therefore offer an ad-hoc participant-initiated phone consultation to discuss the exerciseswith the nurse.

Strengths of this study include community-based recruitment, achievement of data saturation, and cross-validation of data analysis by a trained qualitative researcher (AF). As previously stated, the MRC guidelines for developing and evaluating complex interventions stress the importance of collecting rich and targeted qualitative data to identify potential barriers and facilitators of intervention delivery (Craig et al., 2008), which we achieved through semi-structured interviews with the inclusion of patients who did and did not complete all treatment sessions. This method (semi-structured interviews) is based on data collection "compromise" (Ayala and Elder, 2011). A structured interview may not allow the interviewer to probe further on issues related to the intervention, while an unstructured interview may provide the interviewee with little guidance when responding to questions produced by the interviewer leading to deviation of the discussion. Therefore, we concluded that this method brings the best of both alternatives. Even though individual interviews are less cost-effective, they were preferred over focus groups.

The framework method was preferred and used to analyse data over thematic analysis. The framework method was a good fit for this study as we used the coding framework to explore relevant data under and every subthemes. Data that did not fit within the framework were not coded and therefore not analysed. The framework method made the data analysis more transparent than thematic analysis (Smith and Firth, 2011). In contrast with grounded theory, where the purpose is a theory development from data response (Heath and Cowley, 2004) the framework method, compared and contrasted the cases, allowed the author (PAN) to analyse data during thecollection process, and allowed less experienced researchers (PAN) to use it in a multidisciplinary healthcare research team (Gale et al., 2013).

Face to face, interviews were conducted in the same setting where the intervention was delivered apart from one, which was by telephone. This improves the generalisability of the sample, as this is the setting where behaviours naturally occurred and provide the opportunity to address other contextual factors that informed the intervention (Ayala and

Elder, 2011). However, interviewer bias is more likely to occur in face-to-face interviews compared to telephone interviews as the interviewer may rephrase or adjust the wording of a question to fit the interviewee.

However, there are some caveats to the study. Firstly, the intervention was delivered by a single trained research nurse, and the study was carried out in a research setting. However, the nurse delivering the intervention had no prior experience of treating musculoskeletal disorders, and the participants were recruited from a primary-care-based cohort. These factors increase the transferability of the findings to clinical settings. Secondly, the main interviewer (PAN) also evaluated the fidelity of intervention delivery using video recordings of individual treatment sessions (Hall et al., 2020), which may have affected the line of questioning with participants. However, any risk of bias or judgement in questioning was minimised by conducting interviews at least one week after fidelity assessments and with the use of a pre-specified semi-structured interview.

In conclusion, nurse-led delivery of a non-pharmacological package of care for knee pain is acceptable in a research setting from both nurse and patient perspectives. However, just one research nurse was delivering the intervention, and acceptability may be different for healthcare professionals in other settings. Most people with knee pain were satisfied with the package and found the advice supplied straightforward. The package changed their perception of managing knee pain, understanding that it can be improved through self-management. The results of the study are promising and support the incorporation of the non-pharmacological package of care with minor modification into a feasibility RCT.

5.4.1 Key recommendations

In terms of improving patient engagement, the first recommendation refers to online dietary links that will be inserted in the training manual,accurately addressing the calories of the food labels, as one patient argued that the caloriewebsite he was referred to by the nurse did not correspond to the food labels. Flaws were identified within the description of the exercise sheets, and therefore in the second recommendation, the nurse will be advised to signpost

patients to online sources such asphysio tools, where a more in-depth description and instruction of the body position in a video is displayed. This recommendation aims to prompt treatment enactment, a component of the NIH BCC that was not addressed in the fidelity chapter. Finally, before patient enrolment, the nurse will clarify the purpose of the study to patients and the extentof their involvement in the study (third recommendation). The nurse will need to explain that the study involves learning exercises/weight loss/adjunctive treatments and for the patient to implement and maintain the subsequent lifestyle changes in the long-term to improve knee pain. The nurse should provide regular support and this recommendation also aims to promote treatment enactment. Interestingly, a previous study that developedrecommendations related to fidelity of delivery for people with dementia also highlighted the need to show a video demonstration of the intervention (Walton, 2018). Their study followed methodological steps to develop recommendations based on the behavioural change wheel (Michie et al., 2014). These were: 1) understand the behaviour, 2) identify intervention functions and policy categories, 3) specify intervention content, and 4) identify a mode of delivery. A limitation of our study is that we did not follow these stepsand we only obtained feedback from the key stakeholders (intervention developers, nurses, and patients). However, their study (Walton, 2018) recommends stakeholder feedback before the implementation of these recommendations and this is our key strength.

6. Chapter - Feasibility RCT context

This thesis provided the context in which PAN (the author) conducted an original fidelity assessment. PAN attended all the meetings with the knee pain team and provided input into the development of the non-pharmacological and pharmacological package; however, the intervention was originally developed by Professor A. Abhishek and Dr. Michelle Hall before the PhD commenced. The role of PAN was to develop and conduct a robust evaluation of implementation fidelity and acceptability, and consider its implications for the intervention and conduct of the feasibility RCT. The intervention was revised as a result of fidelity and acceptability assessment but completion of this feasibility RCT was not possible due to COVID. However, it is ongoing. Below, I will be presenting a brief description of the feasibility RCT that I took part during my Ph.D. journey. The sections that I participated are presented below and refer to a brief overview of the RCT, its design, the development of the pharmacological and non-pharmacological package of care alongside with PPI.

6.1 Design of the study

This is a single centre mixed methods feasibility cohort RCT to evaluate a nurse-led complex package of care comprising both pharmacological and non-pharmacological components. Two phases took place. The first phase involved the evaluation of the non- pharmacological package and the identification of issues faced in delivery, while phase two will assess the feasibility of conducting a cohort RCT of a nurse-led intervention comprising of both pharmacological and non-pharmacological elements. PAN wrote the first ethics draft protocol of the overall study and contributed to the design of the study alongside with the acknowledged team.

6.2 Development of the complex package of care

MH, AA, and MD developed the non-pharmacological intervention. The non- pharmacological intervention is a package of care consisting of education, exercise, and weight-loss (if overweight or obese) advice and is based on current best practice guidelines as described by NICE. PPI meetings and a training manual enhanced the development of the non-pharmacological intervention. Simulated consultations with PPI volunteers with knee pain

were trialed for formative assessment of package delivery. Individual feedback was provided to the nurse to further optimise the delivery of the package of care before testing it in the package development phase. The pharmacological intervention is based on an analgesic ladder (Figure 6—1), which aims to optimise analgesia (e.g. topical NSAID gel, oral paracetamol, oral co-codamol (8mg/500mg), topical NSAID cream, oral NSAIDs/COX-II inhibitors). The MRC framework guided the development and evaluation of previous complex intervention packages (Mars et al., 2013, Toomey et al., 2017, Wagland et al., 2012) and therefore, guided the development and evaluation of this study. TEAM Knee Pain meetings were conducted and organised by the project manager (BM) of the study and PAN provided input into the development of the non-pharmacological and pharmacological package.

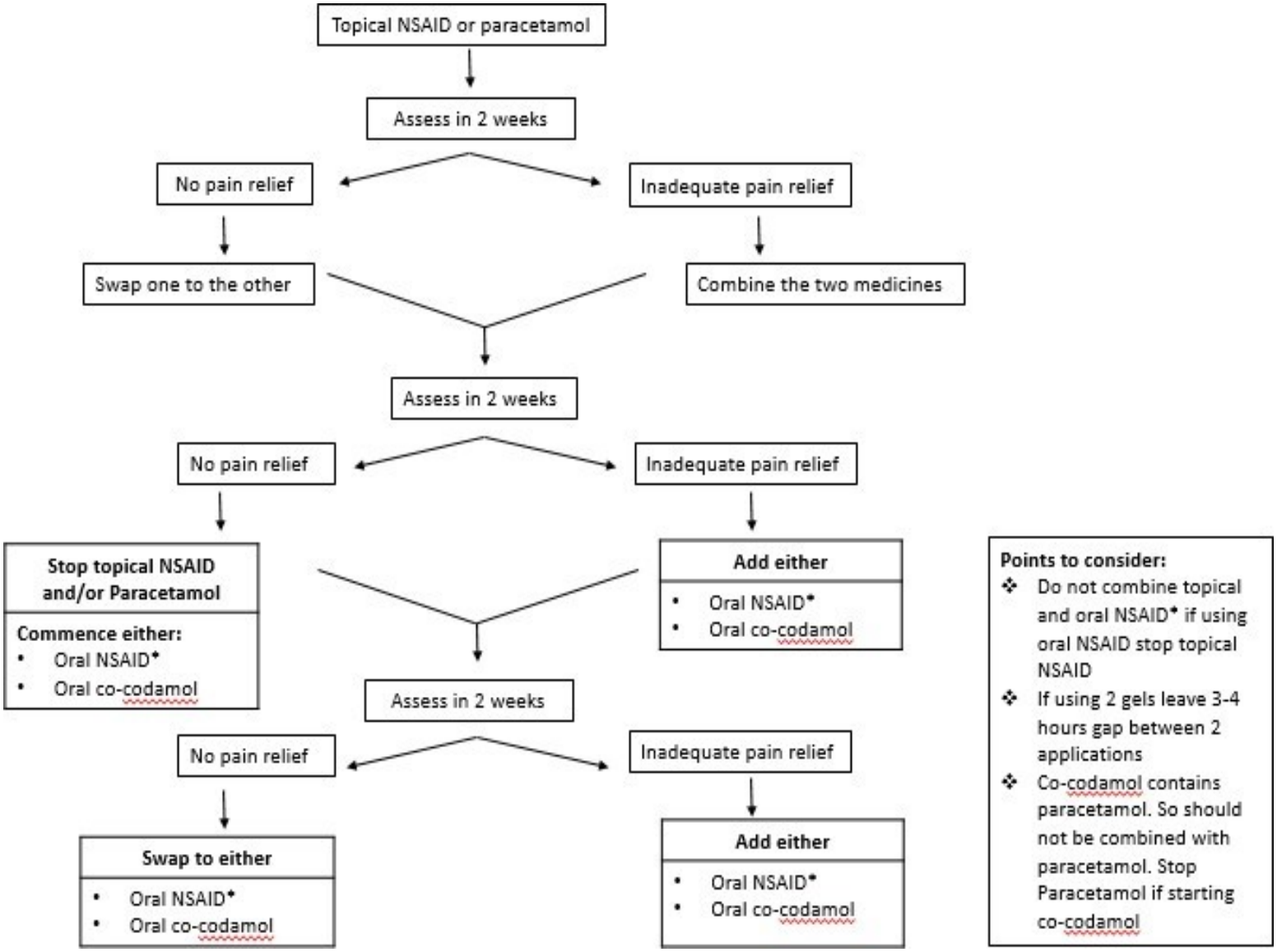


Figure 6—1 Analgesic ladder

6.3 **PPI (Consultation)**

Members of the NIHR Nottingham Biomedical Research Centre (BRC) and Versus ArthritisUK Pain Centre patient and public involvement in a research group with musculoskeletal pain were approached for a PPI meeting. A PPI consultation group meeting was held on the 16th of February 2018 at Academic Rheumatology, City Hospital Nottingham. This meeting was facilitated by MH/BM and attended by PAN. Three female PPI volunteers with knee pain participated in the meeting. Each of them had a range of conditions, different needs, treatment expectations, and experiences regarding physiotherapy, group-based packages, walking groups, drugs, and physical activities. The study was explained to the PPI volunteers and the conversation during the PPI meeting ranged around intervention adherence (activity and food diary and how they will be completed), treatment individualisation (being tailored or group), and treatment sequence (pharmacological or non-pharmacological first and why). Field notes from the PPI meeting were kept and summarised in Appendix I.

6.4 **Overview of the feasibility RCT**

An overview of the East-Midlands knee pain cohort RCT is shown in Figure 6—2.

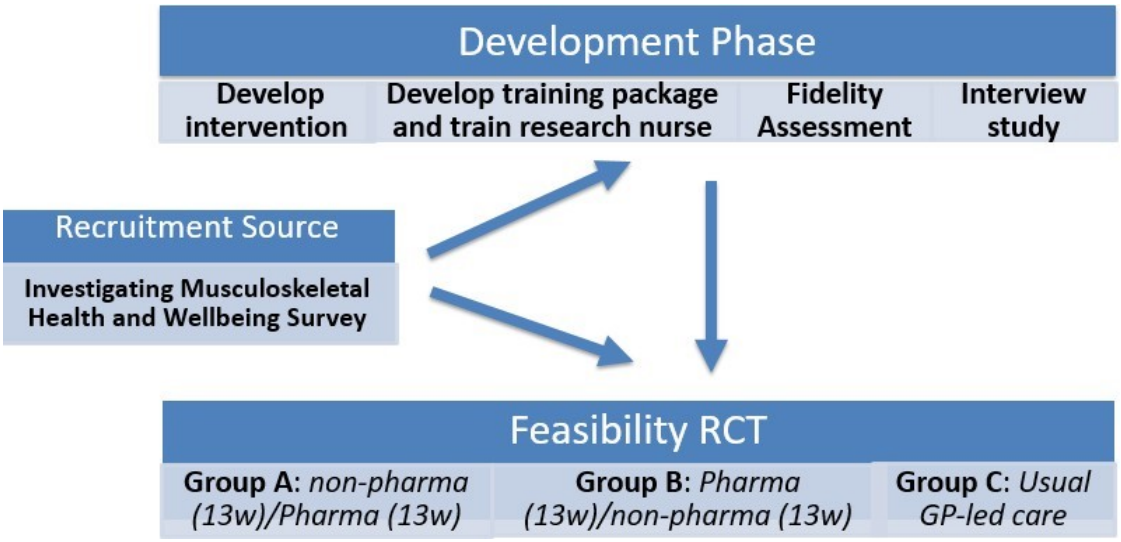


Figure 6—2 Diagram that shows the stages of the package development phase and feasibility RCT

A research nurse delivered the treatment at the NHS site as outline in Table 6-2. Participants were randomised into three arms:

- Group A: Nurse-led non-pharmacologic complex package of care for 13 weeks with stable background analgesia, followed by optimisation of analgesia as recommended by NICE OA guidelines between weeks 13 and 26 as required.
- Group B: Optimisation of analgesia as recommended by NICE OA guidelines for 13 weeks, followed by a nurse-led non-pharmacologic complex package of care between weeks 13 and 26 with optimised background analgesia.
- Group C: Usual care; control group usual care from GP

7. Chapter-Discussion

7.1 Summary of key findings, interpretation, strengths, and caveats

The main aim of this thesis was to evaluate the feasibility of a nurse delivering a complex package of care for knee pain comprising pharmacological and non-pharmacological components. In phase 1, we evaluated the non-pharmacological intervention in the package development phase of the feasibility RCT and identified the specific components of the non-pharmacological intervention not delivered as planned (chapter 4- fidelity of delivery). We also assessed patient and nurse acceptability with the non-pharmacological intervention and resolved issues faced in delivery (chapter 5). The purpose of these was to evaluate the non-pharmacological intervention first and then progress it to a full-scale feasibility RCT. Even though partial data collection took place during the feasibility RCT, this stage was not complete and analysis was not undertaken due to the pandemic.

Although this thesis focused on the fidelity of delivery of, and acceptability with, the non-pharmacological intervention, it was deemed necessary to review and assess the efficacy of previous complex non-pharmacological interventions delivered by any HCP. A key finding was how poorly interventions are reported and how rarely fidelity assessments are done and reported, even though this can moderate outcomes. Therefore,a systematic review and meta-analysis (chapter 2) confirmed poor intervention and fidelity reporting and was conducted and showed that a non-pharmacological package of care for knee pain due to OA comprising at least patient education, exercise, and weight loss advice is more effective than any other single non- pharmacological intervention (e.g. exercise alone) or usual care.

This is the first meta- analysis that assessed the efficacy of complex interventions comprising patient education,exercise, and weight loss advice for knee OA conditions. Twenty studies comprising 3,069 patients with knee OA from different countries were included in this study. The main findings are: [1] a complex intervention is better than usual care with or without any

other single pharmacological/non-pharmacological intervention and showed significant improvements for pain, physical function, and quality of life; [2] most RCTs included in this study did not describe in sufficient detail their intervention and comparator groups. Moderate benefits ES (-0.47, 95% CI -0.77, -0.16) and ES (-0.49, 95% CI -0.72, -0.25), with statistically significant effects for pain (p=0.00) and physical function (p=0.00) outcomes were found respectively. Large benefits ES (2.10, 95% C 1.40, 2.80) with statistically significant effects for quality of life (p=0.03) were found. No evidence of the effect on anxiety and depression was found in this study. The majority of the available evidence (systematic reviews and meta-analyses) published focuses on the effectiveness of physical therapy or exercise and non-pharmacological or non-surgical interventions alone for the management of knee OA (Ferreira et al., 2018, Jamtvedt et al., 2008, Smidtet al., 2005).

The main strength of this systematic review and meta-analysis is that we selected a combination of individual interventions (education, exercise, weight loss advice) and investigated their combined overall treatment effects. This combination of treatments made our intervention complex. However, there were significant clinical, statistical, and methodological variations between and within the included studies. Such variations are to be expected though as a systematic review brings together diverse studies from different methodological and clinical perspectives. Subgroup analyses showed that when we included studies with a high risk of bias in the analysis, the results were very slightly inflated. However, this did not take place for a sample size of more than 100 people and usual care indicating that the pooled results are robust and the wide variability between the studies did not have an impact on the results. This study however did not collect data on the adverse effects of the RCTs included, and this is a significant limitation as it has been shown that land-based exercise for knee OA may increase knee oedema (Røgind et al., 1998), while strengthening exercise may increase knee OA progression in Varus malalignment (Sharma et al., 2003b). Another limitation of our study is that we did not provide detail in terms of which types of exercise, education and weight loss interventions are effective, therefore, a network meta-analysis will be the next future step to investigate and provide evidence in more depth about the individual

combination of these interventions.

This systematic review assessed the completeness of descriptions of non-pharmacological interventions and extended over the general common problem of incomplete description of these also reported by previous studies (Herbert and B∅, 2005). Inadequate description of interventions may reduce the replication of these interventions as the providers may not understand the content of interventions (Duff et al., 2010). This may influence outcome interpretation and process evaluation (Moore et al., 2015a). The findings of our study suggest incomplete reporting of non-pharmacological interventions (chapter 1) and are consistent with previous findings (Hoffmann et al., 2013, Yamato et al., 2016) highlighting significant gaps in intervention reporting in other areas of healthcare as well.A limitation of our study is that we did not contact authors to explore why the interventions were poorly described in these trials.

Finally, this systematic review demonstrated that studies delivering non-pharmacological complex interventions for knee pain due to OA rarely reported both fidelity of delivery and acceptability of non-pharmacological interventions. These findings therefore also highlighted the need to conduct process evaluations in trials and emphasised towards providing greater confidence in conclusions around the effectiveness of interventions by assessing quantity and quality of implementation. Nevertheless, the focus of process evaluation may vary depending on the stage of which is conducted (Moore et al., 2015a).For the purpose of this thesis, process evaluation played a vital role, and optimised the evaluation (chapter 4) and design (chapter 5) of the non-pharmacological intervention, to deliver it to a full-scale feasibility trial.

Fidelity of delivery was measured in the package development phase of the feasibility RCT and findings indicated that most of the non-pharmacological components of the intervention were delivered as planned. To assess fidelity of delivery, we preferred to use video-recordings and provider self-report checklists compared to observations of intervention sessions or audio recordings as these may have affected provider and patient behaviour and caused reactivity

effects (Moncher and Prinz, 1991, French and Sutton, 2010). Indeed, previous findings demonstrated that measuring fidelity using observations and audio recordings may change behaviours of the providers (Walton et al., 2020). Interestingly, Walton et al. (2020) assessed fidelity of delivery of Promoting Independencein Dementia (PRIDE) interventions. Following interviews with the providers, they found out that some of their intervention providers felt quite nervous when the sessions were audio-recorded and felt anxious to complete the fidelity checklists after the sessions tookplace. However, this did not take place in our study but this may be the result of only onenurse delivering the intervention in a single research site. Although, neither the nurse nor the patients raised any concerns being video-recorded and the PPI meetings advised us that video-recordings of the sessions would be deemed as an acceptable alternative. Another advantage is that using video-recordings would help to code the intervention andobserve and rate the sessions multiple times (Walton, 2018).

To measure fidelity of delivery, checklists were developed. The individual components of the fidelity checklist were identified from the intervention manual developed by the study team. Whendeveloping fidelity measures for individualised interventions, attention is needed to clarifywhich components of the intervention are standardised and therefore deliverable to all participants and which are tailored (Haynes et al., 2015). Therefore, assessing the fidelity of an individualised and complex intervention such as this is difficult. The checklist evaluated whether the nurse addressed the key components needed to individualise the intervention. For example, exploring participants' health beliefs including concerns, expectations, and knowledge is required to ensure advice given is individualised. However,assessment of muscle strength and function and discussion of participant goals would be required to individualise exercise selection and prescription. We did not include the prescription of the exercise in the checklist and this is a limitation in our study. To overcome the limitations of the checklist the qualitative interviews (chapter 5) allowed us to explore whether participants perceived that the intervention was individualised to them. Another limitation of our study is that we did not provide specific guidelines on how to score each item on the checklist in contrast with previous studies that developed a detailedintervention framework providing coding guidelines on how

to score each item of their checklist used for dementia interventions (Walton, 2018). However, we integrated the interview findings with the fidelity scores and found convergence for all of them. It is suggested that a combination of multiple methods will provide in-depth fidelity assessment(Toomey et al., 2017).

In addition, we did not assess the acceptability of the fidelity checklist to identify if it meets the target audience in terms of language use. However, our fidelity checklist was based on a previously published fidelity checklist that has been foundfeasible and acceptable to its key stakeholders (Toomey et al., 2016). Their study (Toomey et al., 2016) developed a fidelity protocol and provided recommendations on how to address implementation fidelity in physical therapy-led interventions for chronic low backpain and OA. In our study, the research nurse did not raise any concerns or felt anxious being video-recorded or rating the fidelity checklist.

Fidelity of delivery did not fluctuate much across participants and intervention sessions. While a significant amount of studies suggested that fidelity varied across the providers demonstrating associations between fidelity and provider training or skills, and experiences (Wang et al., 2015, Huijg et al., 2015), our study, could not demonstrate if fidelity is likely to vary across the providers neither quantitatively, nor qualitatively, as there was only one nurse delivering the intervention. However, during the interviews our nurse reflected on her previous experiences working with other patient groups, which facilitated the patient assessment. Other studies highlighted that trial and organisational factors influenced fidelity of delivery, for instance working in a research study might bring changes in the way Occupational Therapists (OTs) work (Masterson-Algar et al., 2014). The latter study investigated fidelity of delivery of OT-led complex intervention and increased the level of independence in personal activities of daily living of stroke patients in UK.

Walton (2018) highlighted the need to monitor inter-rater agreement thorough fidelity assessment and provide clear definitions of the components to make guidelines easier to follow and limit subjectivity in responses of the checklist. The reasons to monitor inter-rater

agreement is because it is difficult to achieve good inter-rater agreement (Harting et al., 2004, Thyrianet al., 2010) and there will be instances where agreement will drop below the required threshold (Walton, 2018). In our study, inter-rater agreement was not monitored on an on-going basis and this is another limitation. Finally, by measuring fidelity using provider self-report checklists and observational methods, fidelity may have been improved. These findings suggest that video—recording the consultations may have changed the way the nurse delivered the interventions to patients.

Taken together, these results show that a complex non-pharmacological intervention for knee OA is effective (chapter 2) and a nurse can deliver the components of a non- pharmacological complex intervention for knee OA with high fidelity (chapter 4). The final chapter, therefore, moves on to discuss the acceptability of the non-pharmacological complex intervention to its recipients: patients (chapter 5). The reason we assessed the acceptability of this non-pharmacological intervention was to understand and clarify the causal mechanisms through which our complex intervention has worked, how it has worked and why.

As stated earlier, acceptability is necessary and should be considered when designing and evaluating complex healthcare interventions (Moore et al.,2015a). However, this was not the only reason we assessed acceptability. A complex healthcare intervention may be delivered with low fidelity from the intervention providers if it is considered to have low acceptability. In addition, if the intervention is not considered acceptable from patients' perspectives, they are less likely to engage with the intervention(Sekhon et al., 2017). Understanding therefore the extent to which participants engage with an intervention is crucial. Although the MRC framework highlights the need to assess the acceptability of complex interventions it does not provide specific definitions for the concept. Our study followed a systematic approach that defined and theorized the concept (Sekhon et al., 2017).

We found that a nurse-led delivery of a non-pharmacological package of care for knee pain is acceptable in a research setting from both nurse and patient perspectives. Participants

found the package of care acceptable and discussed lifestyle changes and factors affecting the delivery of and engagement with the intervention. Lifestyle changes participants made as a result of the intervention were that they had reduced the amount of food they were eating, cut down on alcohol, and increasedphysical activity and exercising. Retired participants had the time to perform the exercisesbut raised concerns that if they were still working they would have found it very difficult to fit it into their lifestyle. Some other changes participants made included swapping alcohol with non-alcoholic beverages and swapping sweets with fruit. Others stopped buying ready meals from the supermarkets. A few stated that the intervention just madesmall adjustments to their existing routines. Participants that were not motivated/prepared enough to make lifestyle changes dropped out of the study. One participant stated that the nurse forced her to have a specific time to perform the exercises. However, the same participant found it very difficult to follow the weight loss advice as had recently lost weight through the weight watchers programme. Another patient that discontinued the study mentioned that they had not realised the extent of involvement required in the study and that this required a complete lifestyle change.

A key strength of our study is that most participants understood how the non-pharmacological intervention works. Considering this, we were able to address intervention coherence with regards to acceptability assessment, and treatment receipt; one of the NIHBCC components that was missing from the fidelity study (chapter 3). We have also interviewed the patients who discontinued the study and identified the causes of discontinuation (burden). This qualitative study also explored patients' perceptions and experiences with previous visits to the doctors and referrals (physiotherapists) and their communication with their HCP against the nurse's package of care. The interview findings revealed the generic apathy towards the knee OA patients by the previous GP / physio visits and are consistent with previous findings where patients reported delays to referralsand were being told by their GP that "nothing could be done" (Sanders et al., 2004, Mann and Gooberman-Hill, 2011).

In our study, the nurse had more time to deliver this non- pharmacological intervention compared with GPs, which might not be the case when this non-pharmacological intervention is delivered in a clinical setting under an increase in demand such as an NHS service. Patients who have seen a physiotherapist in our study reported dissatisfaction with the amount of information provided and a lack of explanationof the prescribed exercise. These findings are consistent with GP-delivered interventions for knee OA (Victor et al., 2004) but contradictory with the findings from a study that explored patient experiences with physiotherapy interventions for knee OA. In the latter study, patients were satisfied and happy with the care they received by their physiotherapists (Teo et al., 2021). However, their study was conducted in Australia, and there were many more females than males who participated. Their participants also were given reimbursement for their time.

Most patients that were prescribed painkillers in our study raised concerns that masking knee pain may create more damage to the joint and this is consistent with the findings by Gignac et al. (2006) who reported patient concerns for curing the symptoms and not the disease. A couple of studies highlighted the need to improve the understanding of patients with knee OA as many have been told that knee OA is likely to deteriorate over time and is part of the normal aging process (Gignac et al.,2006, Turner et al., 2007). Their findings are consistent with our findings as most patients were resigned to the idea that OA will continue getting worse and described the condition as "wear and tear". Paskins et al. (2014) conducted a narrative review of literature detailing patient experiences of consulting with OA in primary care and GP attitudes to, and beliefs about OA. Their review highlighted significant divergence over the management of OA between patient and doctor. Patient studies included, highlighted the negative talks occurring during the consultations; these were negative perceptions of "wear and tear" that may not always originate from the doctor but may originate from the patient perspective. Moreover, GPs reported frustration and lack of knowledge around issues with lifestyle changes. In our study, the nurse was able to discuss and address these lifestyle changes. Moreover, the nurse created a trustworthy relationship with OA patients, which is emphasized of great strategic importance by patients (Alami et al., 2011). GPs felt that the

lack of therapeutic options is what influence the doctor-patient relationship (Coar, 2004).

Factors, which influenced the patient engagement with the non-pharmacological intervention, are identified. A systematic review of qualitative evidence (Kanavaki et al., 2017) identified the barriers and facilitators to physical activity in knee OA. They reported a complex interplay among the physical, intrapersonal psychological, and socio-environmental factors to engagement. They report on some key overlapping themes suchas disease-specific factors, beliefs about the intervention, and social support. Our study extended these factors and included patient education and weight loss as key components of the intervention. Interestingly, we found that the therapist-patient relationship played a vital role in the engagement of the patient to the intervention. The nurse in our study, considered patient treatment preferences, and her input was quite important for patient engagement as patients followed the intervention in the belief that treatment will work. Behavioural change techniques such as goal setting, exercise, and food diaries facilitated engagement as the forms made the patients perform the exercises.

7.2 Implications for practice

Firstly, the research outlined in this thesis used a combination of quantitative and qualitative methodologies to assess fidelity of delivery and acceptability of the interventionand followed the MRC guidance for developing and evaluating complex interventions. Weused a mixed-methods approach, unearthed a comprehensive picture, and understood multiple complex constructs within the delivery of the non-pharmacological intervention. We also followed and addressed all the components of the NIHBCC: study design, training of the providers, treatment delivery, treatment receipt, and treatment enactment. Combining fidelity scores with the interview findings provided insights into how the intervention was delivered as planned. Therefore, this mixed-methods approach can be adopted and used when evaluating the fidelity of delivery of non-pharmacological interventions. Moreover, the individual components of the non-pharmacologicalinterventions that were difficult to deliver as planned are identified, and barriers and facilitators to delivery of the non-pharmacological intervention. Together, these findings along with the recommendations which are: 1) additional complex case studies to nurse's training programme, 2) boosted training sessions with nurses and training developers, 3) provision of online materials to patients, 4) clarification of the purpose of the study and the extent of patient involvement, and 5) regular support to enhance treatment enactment.

The transferability of the method described in chapter 4, suggests that it could potentiallybe applied to evaluate the fidelity of delivery for other healthcare complex interventions.

Secondly, the research outlined in chapter 5, demonstrates that a nurse-led package of care is acceptable from the patient and nurse perspective.

Moreover, the nurse delivering the intervention had no prior experience of treating peoplewith knee OA and the participants were recruited from a primary-care-based cohort. Thesefactors

increase the transferability of the findings to clinical settings. Acceptability was guided by a theoretical framework for acceptability assessment from the perspectives of the nurse and patients. We used semi-structured interviews with patients and the nurse and the analysis revealed minor modifications to the intervention package. This qualitative method (semi-structured interview guides) was developed by the study team can be adapted to be used for exploring other qualitative healthcare research. Moreover, the findings from the analysis provided insights into reasons for dropout rates. The proposed method of assessing acceptability can be applied in the context of a definitive RCT, to assess anticipated and experienced acceptability to the intervention.

Thirdly, a complex package comprised of patient education, exercise, and weight loss addresses the biopsychosocial model and provides a more patient-centred approach to behaviour change which should be prioritized compared with any other individual intervention alone.

Finally, if a nurse-led non-pharmacological package of care is found to be effective and cost-effective this research could inform the extent to which the nurse-led package mightneed to be delivered and how to refine the intervention to achieve this. On the other hand,
if the nurse-led delivery is found ineffective this is due to the intervention content and not because of the poor delivery from the intervention providers. Considering these, policymakers, therefore, can be informed if the interventions are effective and how they should be implemented in larger trials.

7.3 Future research

Future research should consider measuring the fidelity of delivery of more than one nurse delivering a complex intervention in multiple clinical sites (multicentre). Measurement of fidelity and engagement should be considered across different sites and with different providers to make the results more generalizable. The fidelity checklists should provide

specific guidelines on how to score each item of the checklist and monitor inter-rater agreement using Kappa statistics on an ongoing basis. Patient engagement with the non-pharmacological intervention may be measured using self-report data (quantitative measures) as well and these data may be integrated with the findings from the interviewswith patients to provide a more comprehensive insight into the results. The TIDieR checklist should be used to provide a full description of the intervention. Studies that measure acceptability should report all its' key components; affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs, and self- efficacy. Finally, future research should consider the cost-effectiveness of nurse-led delivery services.

8. Chapter-Conclusion

This research assessed the feasibility of a nurse delivering a non-pharmacological packageof care for knee OA. The thesis demonstrated that a trained research nurse could deliver a non-pharmacological package of care, which is found to be effective with high fidelity. The non-pharmacological package of care is found acceptable from nurse and patient perspectives. A complex intervention comprising patient education, exercise and weight loss advice is more effective than any other non-pharmacological intervention, however, network meta-analysis is needed in the future to explore and specify which parts of thecombined interventions are more effective than others.

REFERENCES

ABHISHEK, A. & DOHERTY, M. 2013. Diagnosis and clinical presentation of osteoarthritis. *Rheumatic Disease Clinics,* 39**,** 45-66.

AL-ZAHRANI, K. & BAKHEIT, A. 2002. A study of the gait characteristics of patients with chronic osteoarthritis of the knee. *Disability and rehabilitation,* 24**,** 275-280.

ALAMI, S., BOUTRON, I., DESJEUX, D., HIRSCHHORN, M., MERIC, G., RANNOU, F. & POIRAUDEAU, S. 2011. Patients' and practitioners' views of knee osteoarthritis and its management: a qualitative interview study. *PLoS One,* 6**,** e19634.

ALLEN, J. D., LINNAN, L. A., EMMONS, K. M., BROWNSON, R., COLDITZ, G. & PROCTOR, E. 2012. Fidelity and its relationship to implementation effectiveness, adaptation, and dissemination. *Dissemination and implementation research in health: Translating science to practice***,** 281-304.

ALLEN, K. D., BONGIORNI, D., BOSWORTH, H. B., COFFMAN, C. J., DATTA, S. K., EDELMAN, D., HALL, K. S., LINDQUIST, J. H., ODDONE, E. Z. & HOENIG, H. 2016a. Group Versus Individual Physical Therapy for Veterans With Knee Osteoarthritis: Randomized Clinical Trial. *Physical Therapy,* 96**,** 597-608.

ALLEN, K. D., CHOONG, P. F., DAVIS, A. M., DOWSEY, M. M., DZIEDZIC, K. S., EMERY, C., HUNTER, D. J., LOSINA, E., PAGE, A. E. & ROOS, E. M. 2016b. Osteoarthritis: models for appropriate care across the disease continuum. *Best practice & research Clinical rheumatology,* 30**,** 503-535.

ALLISTON, T., HERNANDEZ, C. J., FINDLAY, D. M., FELSON, D. T. & KENNEDY, O. D. 2018. Bone marrow lesions in osteoarthritis: What lies beneath. *Journal of Orthopaedic Research,* 36**,** 1818-1825.

ALTMAN, R., ASCH, E., BLOCH, D., BOLE, G., BORENSTEIN, D., BRANDT, K., CHRISTY, W., COOKE, T., GREENWALD, R. & HOCHBERG, M. 1986. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology,* 29**,** 1039-1049.

ANDERSEN, R. E., CRESPO, C. J., LING, S. M., BATHON, J. M. & BARTLETT, S. J. 1999. Prevalence of significant knee pain among older Americans: results from the Third National Health and Nutrition Examination Survey. *Journal of the American Geriatrics Society,* 47**,** 1435-1438.

ANG, K., HEPGUL, N., GAO, W. & HIGGINSON, I. J. 2018. Strategies used in improving and assessing the level of reporting of implementation fidelity in randomised controlled trials of palliative care complex interventions: A systematic review. *Palliative medicine,* 32**,** 500-516.

ANTONY, J. 2018. *Automatic quantification of radiographic knee osteoarthritis severity and associated diagnostic features using deep convolutional neural networks.* Dublin City

University.

ARDEN, N. & NEVITT, M. C. 2006. Osteoarthritis: epidemiology. *Best practice & research Clinical rheumatology,* 20**,** 3-25.

ARENDT-NIELSEN, L., NIE, H., LAURSEN, M. B., LAURSEN, B. S., MADELEINE, P., SIMONSEN, O. H. & GRAVEN-NIELSEN, T. 2010. Sensitization in patients with painful knee osteoarthritis. *PAIN,* 149**,** 573-581.

ARMIJO-OLIVO, S., DA COSTA, B. R., CUMMINGS, G. G., HA, C., FUENTES, J., SALTAJI, H. & EGGER, M. 2015. PEDro or Cochrane to Assess the Quality of Clinical Trials? A Meta-Epidemiological Study. *PloS one,* 10**,** e0132634-e0132634.

ASHRAF, S., WIBBERLEY, H., MAPP, P. I., HILL, R., WILSON, D. & WALSH, D. A. 2011. Increased vascular penetration and nerve growth in the meniscus: a potential source of pain in osteoarthritis. *Annals of the rheumatic diseases,* 70**,** 523-529.

ATUKORALA, I., MAKOVEY, J., LAWLER, L., MESSIER, S. P., BENNELL, K. & HUNTER, D. J. 2016. Is there a dose-response relationship between weight loss and symptom improvement in persons with knee osteoarthritis? *Arthritis care & research,* 68**,** 1106-1114.

AYALA, G. X. & ELDER, J. P. 2011. Qualitative methods to ensure acceptability of behavioral and social interventions to the target population. *Journal of public health dentistry,* 71 Suppl 1**,** S69-S79.

BABINEAU, J. 2014. Product review: covidence (systematic review software). *Journal of the Canadian Health Libraries Association/Journal de l'Association des bibliothèques de la santé du Canada,* 35**,** 68-71.

BAGGE, E., BJELLE, A., EDEN, S. & SVANBORG, A. 1992. A longitudinal study of the occurrence of joint complaints in elderly people. *Age and ageing,* 21**,** 160-167.

BANGERT-DROWNS, R. L., WELLS-PARKER, E. & CHEVILLARD, I. 1997. Assessing the methodological quality of research in narrative reviews and meta-analyses.

BARTELS, E. M., JUHL, C. B., CHRISTENSEN, R., HAGEN, K. B., DANNESKIOLD-SAMSØE, B., DAGFINRUD, H. & LUND, H. 2016. Aquatic exercise for the treatment of knee and hip osteoarthritis. *Cochrane Database of Systematic Reviews*.

BECKER, W. C., DORFLINGER, L., EDMOND, S. N., ISLAM, L., HEAPY, A. A. & FRAENKEL, L. 2017. Barriers and facilitators to use of non-pharmacological treatments in chronic pain. *BMC family practice,* 18**,** 41.

BEDSON, J. & CROFT, P. R. 2008. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. *BMC musculoskeletal disorders,* 9**,** 1-11.

BELLG, A. J., BORRELLI, B., RESNICK, B., HECHT, J., MINICUCCI, D. S., ORY, M., OGEDEGBE, G., ORWIG, D., ERNST, D. & CZAJKOWSKI, S. 2004. Enhancing treatment fidelity in health behavior change studies: best practices and recommendations from the NIH Behavior Change Consortium. *Health Psychology,* 23**,** 443.

BENJAMINI, Y. & HOCHBERG, Y. 1995. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society. Series B (Methodological),* 57**,** 289-300.

BENNELL, K. L., KEATING, C., LAWFORD, B. J., KIMP, A. J., EGERTON, T., BROWN, C., KASZA, J., SPIERS, L., PROIETTO, J., SUMITHRAN, P., QUICKE, J. G., HINMAN, R. S., BETTER KNEE, B. M. T. M. S. T., HARRIS, A., BRIGGS, A. M., PAGE, C., CHOONG, P. F., DOWSEY, M. M., KEEFE, F. & RINI, C. 2020. Better Knee, Better Me TM: effectiveness of two scalable health care interventions supporting self-management for knee osteoarthritis - protocol for a randomized controlled trial. *BMC Musculoskeletal Disorders,* 21**,** 160.

BENNELL, K. L., NELLIGAN, R., DOBSON, F., RINI, C., KEEFE, F., KASZA, J., FRENCH, S., BRYANT, C., DALWOOD, A., ABBOTT, J. H. & HINMAN, R. S. 2017. Internet-delivered exercise and pain-coping skills training for chronic knee pain. *Annals of Internal Medicine,* 166**,** I13.

BIJLSMA, J. W., BERENBAUM, F. & LAFEBER, F. P. 2011. Osteoarthritis: an update with relevance for clinical practice. *The Lancet,* 377**,** 2115-2126.

BIJSTERBOSCH, J., SCHARLOO, M., VISSER, A. W., WATT, I., MEULENBELT, I., HUIZINGA, T. W. J., KAPTEIN, A. A. & KLOPPENBURG, M. 2009. Illness perceptions in patients with osteoarthritis: Change over time and association with disability. *Arthritis Care & Research,* 61**,** 1054-1061.

BLAGOJEVIC, M., JINKS, C., JEFFERY, A. & JORDAN, K. 2010. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis and cartilage,* 18**,** 24-33.

BONELL, C., FLETCHER, A., MORTON, M., LORENC, T. & MOORE, L. 2012. Realist randomised controlled trials: a new approach to evaluating complex public health interventions. *Social science & medicine,* 75**,** 2299-2306.

BORENSTEIN, M., HEDGES, L. V., HIGGINS, J. P. & ROTHSTEIN, H. R. 2021. *Introduction to meta-analysis*, John Wiley & Sons.

BORRELLI, B. 2011. The assessment, monitoring, and enhancement of treatment fidelity in public health clinical trials. *Journal of public health dentistry,* 71**,** S52-S63.

BORRELLI, B., SEPINWALL, D., ERNST, D., BELLG, A. J., CZAJKOWSKI, S., BREGER, R., DEFRANCESCO, C., LEVESQUE, C., SHARP, D. L. & OGEDEGBE, G. 2005. A new tool to assess treatment fidelity and evaluation of treatment fidelity across 10 years of health behavior research. *Journal of consulting and clinical psychology,* 73**,** 852.

BRAMER, W. M., DE JONGE, G. B., RETHLEFSEN, M. L., MAST, F. & KLEIJNEN, J. 2018. A systematic approach to searching: an efficient and complete method to develop literature searches. *Journal of the Medical Library Association : JMLA,* 106**,** 531-541.

BOTHA-SCHEEPERS, S., RIYAZI, N., KROON, H. M., SCHARLOO, M., HOUWING DUISTERMAAT, J. J., SLAGBOOM, E., ROSENDAAL, F. R., BREEDVELD, F. C. & KLOPPENBURG, M. 2006. Activity limitations in the lower extremities in patients with osteoarthritis: the modifying effects of illness perceptions and mental health. *Osteoarthritis and Cartilage,* 14**,** 1104-1110.

CAMPBELL, M., FITZPATRICK, R., HAINES, A., KINMONTH, A. L., SANDERCOCK, P., SPIEGELHALTER, D. & TYRER, P. 2000. Framework for design and evaluation of complex interventions to improve health. *BMJ (Clinical research ed.),* 321**,** 694-696.

CARR, A. J., ROBERTSSON, O., GRAVES, S., PRICE, A. J., ARDEN, N. K., JUDGE, A. & BEARD, D. J. 2012. Knee replacement. *The Lancet,* 379**,** 1331-1340.

CARROLL, C., PATTERSON, M., WOOD, S., BOOTH, A., RICK, J. & BALAIN, S. 2007. A conceptual framework for implementation fidelity. *Implementation Science,* 2**,** 40.

CHAN, K. K. W., SIT, R. W. S., WU, R. W. K. & NGAI, A. H. Y. 2014. Clinical, Radiological and Ultrasonographic Findings Related to Knee Pain in Osteoarthritis. *PLOS ONE,* 9**,** e92901.

CHEN, A., GUPTE, C., AKHTAR, K., SMITH, P. & COBB, J. 2012. The global economic cost of osteoarthritis: how the UK compares. *Arthritis,* 2012.

COAR, L. 2004. General Practitioners' understanding and perceptions of osteoarthritis: an exploratory study. *UK: MPhil Thesis. Keele University*.

COGGON, D., CROFT, P., KELLINGRAY, S., BARRETT, D., MCLAREN, M. & COOPER, C. 2000. Occupational physical activities and osteoarthritis of the knee. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology,* 43**,** 1443-1449.

COLDITZ, G. A. & EMMONS, K. M. 2012. The promise and challenges of dissemination and implementation research. *Dissemination and implementation research in health: Translating science to practice***,** 3-22.

COLEMAN, S., BRIFFA, N. K., CARROLL, G., INDERJEETH, C., COOK, N. & MCQUADE, J. 2012. A randomised controlled trial of a self-management education program for osteoarthritis of the knee delivered by health professionals. *Arthritis Research & Therapy***,** R21.

CONAGHAN, P. G., DICKSON, J. & GRANT, R. L. 2008. Care and management of osteoarthritis in adults: summary of NICE guidance. *Bmj,* 336**,** 502-503.

CRAIG, P., DIEPPE, P., MACINTYRE, S., MICHIE, S., NAZARETH, I. & PETTICREW, M. 2008. Developing and evaluating complex interventions: the new Medical Research Council guidance. *Bmj,* 337.

CREAMER, P., LETHBRIDGE-CEJKU, M., COSTA, P., TOBIN, J. D., HERBST, J. H. & HOCHBERG, M. C. 1999. The relationship of anxiety and depression with self-reported knee pain in the community: data from the Baltimore Longitudinal Study of Aging. *Arthritis Care & Research,* 12**,** 3-7.

CROSS, M., SMITH, E., HOY, D., NOLTE, S., ACKERMAN, I., FRANSEN, M., BRIDGETT, L., WILLIAMS, S., GUILLEMIN, F. & HILL, C. L. 2014. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Annals of the rheumatic diseases,* 73**,** 1323-1330.

CUI, A., LI, H., WANG, D., ZHONG, J., CHEN, Y. & LU, H. 2020. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. *EClinicalMedicine,* 29.

CULLIFORD, D., MASKELL, J., JUDGE, A., COOPER, C., PRIETO-ALHAMBRA, D., ARDEN, N. & GROUP, C. S. 2015. Future projections of total hip and knee arthroplasty in the UK: results from the UK Clinical Practice Research Datalink. *Osteoarthritis and cartilage,* 23**,** 594-600.

DA COSTA, B. R., HILFIKER, R. & EGGER, M. 2013. PEDro's bias: summary quality scores

should not be used in meta-analysis. *Journal of clinical epidemiology,* 66**,** 75-77.

DA SILVA, F. S., DE MELO, F. E., DO AMARAL, M. M., CALDAS, V. V., PINHEIRO, I. L., ABREU, B. J. & VIEIRA, W. H. 2015. Efficacy of simple integrated group rehabilitation program for patients with knee osteoarthritis: Single-blind randomized controlled trial. *Journal of Rehabilitation Research & Development,* 52**,** 309-22.

DAVIS, M., ETTINGER, W., NEUHAUS, J., BARCLAY, J. & SEGAL, M. 1992. Correlates of knee pain among US adults with and without radiographic knee osteoarthritis. *The Journal of rheumatology,* 19**,** 1943-1949.

DAWSON, J., JUSZCZAK, E., THOROGOOD, M., MARKS, S., DODD, C. & FITZPATRICK, R. 2003. An investigation of risk factors for symptomatic osteoarthritis of the knee in women using a life course approach. *Journal of Epidemiology & Community Health,* 57**,** 823-830.

DE REZENDE, M. U., DE CAMPOS, G. C., FRUCCHI, R., PASQUALIN, T. & DE CAMARGO, O. P. 2013. PARQVE-project arthritis recovering quality of life by means of education short-term outcome in a randomized clinical trial. *Journal of Arthritis,* 2**,** 1-6.

DE REZENDE, M. U., HISSADOMI, M. I., DE CAMPOS, G. C., FRUCCHI, R., PAILO, A. F., PASQUALIN, T., BRITO, N. L. R., SANTANA, O. F. M., MOREIRA, M. M. & STRUTZ, C. G. 2016. One-year results of an educational program on osteoarthritis: a prospective randomized controlled trial in brazil. *Geriatric orthopaedic surgery & rehabilitation,* 7**,** 86-94.

DENVER, E. A., BARNARD, M., WOOLFSON, R. G. & EARLE, K. A. 2003. Management of uncontrolled hypertension in a nurse-led clinic compared with conventional care for patients with type 2 diabetes. *Diabetes care,* 26**,** 2256-2260.

DICICCO-BLOOM, B. & CRABTREE, B. F. 2006. The qualitative research interview. *Medical Education,* 40**,** 314-321.

DIEPPE, P., LIM, K. & LOHMANDER, S. 2011. Who should have knee joint replacement surgery for osteoarthritis? *International journal of rheumatic diseases,* 14**,** 175-180.

DIEPPE, P. A., CUSHNAGHAN, J. & SHEPSTONE, L. 1997. The Bristol 'OA500'study: progression of osteoarthritis (OA) over 3 years and the relationship between clinical and radiographic changes at the knee joint. *Osteoarthritis and Cartilage,* 5**,** 87-97.

DIERICK-VAN DAELE, A. T., STEUTEN, L. M., METSEMAKERS, J. F., DERCKX, E. W., SPREEUWENBERG, C. & VRIJHOEF, H. J. 2010. Economic evaluation of nurse practitioners versus GPs in treating common conditions. *Br J Gen Pract,* 60**,** e28-e35.

DOHERTY, M. 2001. Risk factors for progression of knee osteoarthritis. *The Lancet,* 358**,** 775-776.

DOHERTY, M., JENKINS, W., RICHARDSON, H., SARMANOVA, A., ABHISHEK, A., ASHTON, D., BARCLAY, C., DOHERTY, S., DULEY, L. & HATTON, R. 2018. Efficacy and cost-effectiveness of nurse-led care involving education and engagement of patients and a treat-to-target urate-lowering strategy versus usual care for gout: a randomised controlled trial. *The Lancet,* 392**,** 1403-1412.

DRISCOLL, A., CURREY, J., TONKIN, A. & KRUM, H. 2015. Nurse-led titration of angiotensin converting enzyme inhibitors, beta-adrenergic blocking agents, and angiotensin receptor blockers for people with heart failure with reduced ejection fraction.

DUFF, J. M., LEATHER, H., WALDEN, E. O., LAPLANT, K. D. & GEORGE, T. J. 2010. Adequacy of published oncology randomized controlled trials to provide therapeutic details needed for clinical application. *Jnci: Journal Of The National Cancer Institute,* 102**,** 702-705.

DUNCAN, R., PEAT, G., THOMAS, E., HAY, E., MCCALL, I. & CROFT, P. 2007. Symptoms and radiographic osteoarthritis: not as discordant as they are made out to be? *Annals of the rheumatic diseases,* 66**,** 86-91.

DUSENBURY, L., BRANNIGAN, R., FALCO, M. & HANSEN, W. B. 2003. A review of research on fidelity of implementation: implications for drug abuse prevention in school settings. *Health Educ Res,* 18**,** 237-56.

DZIEDZIC, K., HEALEY, E. & MAIN, C. 2013. Implementing the NICE osteoarthritis guidelines in primary care: a role for practice nurses. *Musculoskeletal Care,* 11**,** 1-2.

DZIEDZIC, K. S., HEALEY, E. L., PORCHERET, M., ONG, B. N., MAIN, C. J., JORDAN, K. P., LEWIS, M., EDWARDS, J. J., JINKS, C. & MORDEN, A. 2014. Implementing the NICE osteoarthritis guidelines: a mixed methods study and cluster randomised trial of a model osteoarthritis consultation in primary care-the Management of OsteoArthritis In Consultations (MOSAICS) study protocol. *Implementation Science,* 9**,** 1-15.

EGERTON, T., DIAMOND, L., BUCHBINDER, R., BENNELL, K. & SLADE, S. C. 2017. A systematic review and evidence synthesis of qualitative studies to identify primary care clinicians' barriers and enablers to the management of osteoarthritis. *Osteoarthritis and cartilage,* 25**,** 625-638.

EGERTON, T., NELLIGAN, R. K., SETCHELL, J., ATKINS, L. & BENNELL, K. L. 2018. General practitioners' views on managing knee osteoarthritis: a thematic analysis of factors influencing clinical practice guideline implementation in primary care. *BMC rheumatology,* 2**,** 30.

EGGER, M., JUNI, P., BARTLETT, C., HOLENSTEIN, F. & STERNE, J. 2003. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. *Health Technol Assess,* 7**,** 1-76.

ELDRIDGE, S. M., LANCASTER, G. A., CAMPBELL, M. J., THABANE, L., HOPEWELL, S., COLEMAN, C. L. & BOND, C. M. 2016. Defining Feasibility and Pilot Studies in Preparation for Randomised Controlled Trials: Development of a Conceptual Framework. *PLoS ONE,* 11**,** e0150205.

EYLES, J. P., LUCAS, B. R., PATTERSON, J. A., WILLIAMS, M. J., WEEKS, K., FRANSEN, M. & HUNTER, D. J. 2014. Does clinical presentation predict response to a nonsurgical chronic disease management program for endstage hip and knee osteoarthritis? *The Journal of rheumatology,* 41**,** 2223-2231.

FARMER, T., ROBINSON, K., ELLIOTT, S. J. & EYLES, J. 2006. Developing and implementing a triangulation protocol for qualitative health research. *Qualitative health research,* 16**,** 377-394.

FARR, J. N., GOING, S. B., MCKNIGHT, P. E., KASLE, S., CUSSLER, E. C. & CORNETT, M. 2010. Progressive resistance training improves overall physical activity levels in patients with early osteoarthritis of the knee: a randomized controlled trial. *Physical therapy,* 90**,** 356-366.

FARRELL, M. J., GIBSON, S. J., MCMEEKEN, J. M. & HELME, R. D. 2000. Increased movement pain in osteoarthritis of the hands is associated with Aβ-mediated cutaneous mechanical sensitivity. *The Journal of Pain,* 1**,** 229-242.

FELSON, D. T. 1988. Epidemiology of hip and knee osteoarthritis. *Epidemiologic reviews,* 10**,** 1-28.

FELSON, D. T. 2009. Developments in the clinical understanding of osteoarthritis. *Arthritis research & therapy,* 11**,** 1-11.

FELSON, D. T., LAWRENCE, R. C., DIEPPE, P. A. & ET AL. 2000. Osteoarthritis: New insights. part 1: the disease and its risk factors. *Annals of Internal Medicine,* 133**,** 635-646.

FELSON, D. T., NAIMARK, A., ANDERSON, J., KAZIS, L., CASTELLI, W. & MEENAN, R. F. 1987. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis & Rheumatology,* 30**,** 914-918.

FELSON, D. T., ZHANG, Y., HANNAN, M. T., NAIMARK, A., WEISSMAN, B., ALIABADI, P. & LEVY, D. 1997. Risk factors for incident radiographic knee osteoarthritis in the elderly. The Framingham Study. *Arthritis & Rheumatism,* 40**,** 728-733.

FERNANDES, G. S., PAREKH, S. M., MOSES, J., FULLER, C., SCAMMELL, B., BATT, M. E., ZHANG, W. & DOHERTY, M. 2018. Prevalence of knee pain, radiographic osteoarthritis and arthroplasty in retired professional footballers compared with men in the general population: a cross-sectional study. *British journal of sports medicine,* 52**,** 678-683.

FERREIRA, R. M., DUARTE, J. A. & GONÇALVES, R. S. 2018. Non-pharmacological and non-surgical interventions to manage patients with knee osteoarthritis: an umbrella review. *Acta Reumatol Port,* 43**,** 182-200.

FISHER, P., MCCARNEY, R., HASFORD, C. & VICKERS, A. 2006. Evaluation of specific and non-specific effects in homeopathy: feasibility study for a randomised trial. *Homeopathy,* 95**,** 215-222.

FLICK, U. 2014. *AN INTRODUCTION TO QUALITATIVE RESEARCH,* London SAGE Publications Ltd.

FRENCH, D. P. & SUTTON, S. 2010. Reactivity of measurement in health psychology: how much of a problem is it? What can be done about it? *British journal of health psychology,* 15**,** 453-468.

FRENCH, S. D., GREEN, S. E., FRANCIS, J. J., BUCHBINDER, R., O'CONNOR, D. A., GRIMSHAW, J. M. & MICHIE, S. 2015. Evaluation of the fidelity of an interactive face-to-face educational intervention to improve general practitioner management of back pain. *BMJ open,* 5**,** e007886.

FULLER, A., JENKINS, W., DOHERTY, M. & ABHISHEK, A. 2019. Nurse-led care is preferred over GP-led care of gout and improves gout outcomes: results of Nottingham Gout Treatment Trial follow-up study. *Rheumatology (Oxford)*.

GALE, N. K., HEATH, G., CAMERON, E., RASHID, S. & REDWOOD, S. 2013. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC medical research methodology,* 13**,** 1-8.

GALLACHER, K., MAY, C. R., MONTORI, V. M. & MAIR, F. S. 2011. Understanding patients' experiences of treatment burden in chronic heart failure using normalization process theory. *The Annals of Family Medicine,* 9**,** 235-243.

GIGNAC, M. A., DAVIS, A. M., HAWKER, G., WRIGHT, J. G., MAHOMED, N., FORTIN, P. R. & BADLEY, E. M. 2006. "What do you expect? You're just getting older": a comparison of perceived osteoarthritis-related and aging-related health experiences in middle-and older-age adults. *Arthritis Care & Research: Official Journal of the American College of Rheumatology,* 55**,** 905-912.

GIVEN, L. M. 2008. *The Sage encyclopedia of qualitative research methods*, Sage Publications.

GOH, S.-L., PERSSON, M. S. M., STOCKS, J., HOU, Y., LIN, J., HALL, M. C., DOHERTY, M. & ZHANG, W. 2019. Efficacy and potential determinants of exercise therapy in knee and hip osteoarthritis: A systematic review and meta-analysis. *Annals of Physical and Rehabilitation Medicine,* 62**,** 356-365.

GOHIR, S. A., EEK, F., KELLY, A., ABHISHEK, A. & VALDES, A. M. 2021. Effectiveness of Internet-Based Exercises Aimed at Treating Knee Osteoarthritis: The iBEAT-OA Randomized Clinical Trial. *JAMA network open,* 4**,** e210012-e210012.

GOLDRING, M. B. & MARCU, K. B. 2009. Cartilage homeostasis in health and rheumatic diseases. *Arthritis research & therapy,* 11**,** 1-16.

GOLDRING, M. B. & OTERO, M. 2011. Inflammation in osteoarthritis. *Current opinion in rheumatology,* 23**,** 471.

GREENHALGH, T., HINTON, L., FINLAY, T., MACFARLANE, A., FAHY, N., CLYDE, B. & CHANT, A. 2019. Frameworks for supporting patient and public involvement in research: Systematic review and co-design pilot. *Health Expectations,* 22**,** 785-801.

GROL, R. & WENSING, M. 2004. What drives change? Barriers to and incentives for achieving evidence-based practice. *Medical Journal of Australia,* 180**,** S57.

GROTLE, M., HAGEN, K. B., NATVIG, B., DAHL, F. A. & KVIEN, T. K. 2008. Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up. *BMC musculoskeletal disorders,* 9**,** 132.

GUERMAZI, A., NIU, J., HAYASHI, D., ROEMER, F. W., ENGLUND, M., NEOGI, T., ALIABADI, P., MCLENNAN, C. E. & FELSON, D. T. 2012. Prevalence of abnormalities in knees detected by MRI in adults without knee osteoarthritis: population based observational study (Framingham Osteoarthritis Study). *Bmj,* 345.

GUEST, G., BUNCE, A. & JOHNSON, L. 2006. How many interviews are enough? An experiment with data saturation and variability. *Field methods,* 18**,** 59-82.

HALL, M., FULLER, A., NOMIKOS, P. A., MILLAR, B., OGOLLAH, R., VALDES, A., GREENHAFF, P., DAS NAIR, R., DOHERTY, M., WALSH, D. A. & ABHISHEK, A. 2020. East Midlands knee pain multiple randomised controlled trial cohort study: cohort establishment and feasibility study protocol. *BMJ Open,* 10**,** e037760.

HAMPSON, S. E., GLASGOW, R. E. & ZEISS, A. M. 1994. Personal models of osteoarthritis and their relation to self-management activities and quality of life. *Journal of Behavioral Medicine,* 17**,** 143-158.

HARDEMAN, W., MICHIE, S., FANSHAWE, T., PREVOST, A. T., MCLOUGHLIN, K. & KINMONTH, A. L. 2008. Fidelity of delivery of a physical activity intervention: predictors and consequences. *Psychology and Health,* 23**,** 11-24.

HARRIS, A. D., MCGREGOR, J. C., PERENCEVICH, E. N., FURUNO, J. P., ZHU, J., PETERSON, D. E. & FINKELSTEIN, J. 2006. The use and interpretation of quasi-experimental studies in medical informatics. *Journal of the American Medical Informatics Association : JAMIA,* 13**,** 16-23.

HART, D. J., DOYLE, D. V. & SPECTOR, T. D. 1999. Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women. *Arthritis Rheum,* 42**,** 17-24.

HARTING, J., VAN ASSEMA, P., VAN DER MOLEN, H. T., AMBERGEN, T. & DE VRIES, N. K. 2004. Quality assessment of health counseling: performance of health advisors in cardiovascular prevention. *Patient Education and Counseling,* 54**,** 107-118.

HAWKER, G., STEWART, L., FRENCH, M., CIBERE, J., JORDAN, J., MARCH, L., SUAREZ-ALMAZOR, M. & GOOBERMAN-HILL, R. 2008. Understanding the pain experience in hip and knee osteoarthritis–an OARSI/OMERACT initiative. *Osteoarthritis and Cartilage,* 16**,** 415-422.

HAWKER, G. A., WRIGHT, J. G., COYTE, P. C., WILLIAMS, J. I., HARVEY, B., GLAZIER, R. & BADLEY, E. M. 2000. Differences between men and women in the rate of use of hip and knee arthroplasty. *New England Journal of Medicine,* 342**,** 1016-1022.

HAY, E. M., FOSTER, N. E., THOMAS, E., PEAT, G., PHELAN, M., YATES, H. E., BLENKINSOPP, A. & SIM, J. 2006. Effectiveness of community physiotherapy and enhanced pharmacy review for knee pain in people aged over 55 presenting to primary care: pragmatic randomised trial. *Bmj,* 333**,** 995.

HAYNES, A., BRENNAN, S., REDMAN, S., WILLIAMSON, A., GALLEGO, G. & BUTOW, P. 2015. Figuring out fidelity: a worked example of the methods used to identify, critique and revise the essential elements of a contextualised intervention in health policy agencies. *Implementation Science,* 11**,** 1-18.

HEATH, H. & COWLEY, S. 2004. Developing a grounded theory approach: a comparison of Glaser and Strauss. *International journal of nursing studies,* 41**,** 141-150.

HEDGES, L. V. & OLKIN, I. 2014. *Statistical methods for meta-analysis*, Academic press.

HERBERT, R. D. & B∅, K. 2005. Analysis of quality of interventions in systematic reviews. *BMJ,* 331**,** 507-509.

HERNÁNDEZ-MOLINA, G., NEOGI, T., HUNTER, D. J., NIU, J., GUERMAZI, A., REICHENBACH, S., ROEMER, F. W., MCLENNAN, C. E. & FELSON, D. T. 2008. The association of bone attrition with knee pain and other MRI features of osteoarthritis. *Annals of the Rheumatic Diseases,* 67**,** 43-47.

HIGGINS, T., CHADLER, CUMPSON, LI, PAGE, WELCH (ed.) 2021. *Cochrane Handbook for Systematic Reviews of Interventions*: Cochrane.

HILL, S., DZIEDZIC, K., THOMAS, E., BAKER, S. & CROFT, P. 2007. The illness perceptions associated with health and behavioural outcomes in people with musculoskeletal hand problems: findings from the North Staffordshire Osteoarthritis Project (NorStOP).

HOCHBERG, M. C. 1996. Prognosis of osteoarthritis. *Annals of the rheumatic diseases,* 55**,** 685.

HOCHBERG, M. C., ALTMAN, R. D., APRIL, K. T., BENKHALTI, M., GUYATT, G., MCGOWAN, J., TOWHEED, T., WELCH, V., WELLS, G. & TUGWELL, P. 2012. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis care & research,* 64**,** 465-474.

HOFFMANN, T. C., ERUETI, C. & GLASZIOU, P. P. 2013. Poor description of non-pharmacological interventions: analysis of consecutive sample of randomised trials. *Bmj,* 347.

HOFFMANN, T. C., GLASZIOU, P. P., BOUTRON, I., MILNE, R., PERERA, R., MOHER, D., ALTMAN, D. G., BARBOUR, V., MACDONALD, H., JOHNSTON, M., LAMB, S. E., DIXON-WOODS, M., MCCULLOCH, P., WYATT, J. C., CHAN, A.-W. & MICHIE, S. 2014. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ : British Medical Journal,* 348**,** g1687.

HOMMEL, K. A., HENTE, E., HERZER, M., INGERSKI, L. M. & DENSON, L. A. 2013. Telehealth behavioral treatment for medication nonadherence: a pilot and feasibility study. *European journal of gastroenterology & hepatology,* 25**,** 469.

HUIJG, J. M., DUSSELDORP, E., GEBHARDT, W. A., VERHEIJDEN, M. W., VAN DER ZOUWE, N., MIDDELKOOP, B. J., DUIJZER, G. & CRONE, M. R. 2015. Factors associated with physical therapists' implementation of physical activity interventions in the Netherlands. *Physical therapy,* 95**,** 539-557.

HUNTER, D. J., MCDOUGALL, J. J. & KEEFE, F. J. 2008. The symptoms of osteoarthritis and the genesis of pain. *Rheumatic diseases clinics of North America,* 34**,** 623-643.

HURLEY, M. & WALSH, N. E. 2012. Long term costs and cost-effectiveness of an integrated rehabilitation programme for chronic knee pain. *Arthritis and Rheumatism,* 10)**,** S675-S676.

IBRAHIM, S. & SIDANI, S. 2015. Fidelity of intervention implementation: a review of instruments. *Health,* 7**,** 1687.

IM, H. J., KIM, J. S., LI, X., KOTWAL, N., SUMNER, D. R., VAN WIJNEN, A. J., DAVIS, F. J., YAN, D., LEVINE, B. & HENRY, J. L. 2010. Alteration of sensory neurons and spinal response to an experimental osteoarthritis pain model. *Arthritis & Rheumatism,* 62**,** 2995-3005.

INGHAM, S., ZHANG, W., DOHERTY, S., MCWILLIAMS, D., MUIR, K. & DOHERTY, M. 2011. Incident knee pain in the Nottingham community: a 12-year retrospective cohort study. *Osteoarthritis and cartilage,* 19**,** 847-852.

JACQUIER, I., BOUTRON, I., MOHER, D., ROY, C. & RAVAUD, P. 2006. The reporting of randomized clinical trials using a surgical intervention is in need of immediate improvement: a systematic review. *Annals of surgery,* 244**,** 677.

JAMSHED, S. 2014. Qualitative research method-interviewing and observation. *Journal of basic and clinical pharmacy,* 5**,** 87-88.

JAMTVEDT, G., DAHM, K. T., CHRISTIE, A., MOE, R. H., HAAVARDSHOLM, E., HOLM, I. & HAGEN, K. B. 2008. Physical Therapy Interventions for Patients With Osteoarthritis of the Knee: An Overview of Systematic Reviews. *Physical Therapy,* 88**,** 123-136.

JELLEY, W., LAROCQUE, N. & PATTERSON, S. 2010. Intradisciplinary clinical education for physiotherapists and physiotherapist assistants: a pilot study. *Physiotherapy Canada.*

Physiotherapie Canada, 62**,** 75-80.

JINKS, C., JORDAN, K., BLAGOJEVIC, M. & CROFT, P. 2008. Predictors of onset and progression of knee pain in adults living in the community. A prospective study. *Rheumatology,* 47**,** 368-374.

JINKS, C., JORDAN, K., ONG, B. & CROFT, P. 2003. A brief screening tool for knee pain in primary care (KNEST). 2. Results from a survey in the general population aged 50 and over. *Rheumatology,* 43**,** 55-61.

JOBE, J. B. 2003. Cognitive psychology and self-reports: models and methods. *Quality of Life Research,* 12**,** 219-227.

JORDAN, J. M., LUTA, G., RENNER, J. B., LINDER, G. F., DRAGOMIR, A., HOCHBERG, M. C. & FRYER, J. G. 1996. Self-reported functional status in osteoarthritis of the knee in a rural southern community: the role of sociodemographic factors, obesity, and knee pain. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology,* 9**,** 273-278.

JORDAN, K., ARDEN, N., DOHERTY, M., BANNWARTH, B., BIJLSMA, J., DIEPPE, P., GUNTHER, K., HAUSELMANN, H., HERRERO-BEAUMONT, G. & KAKLAMANIS, P. 2003. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Annals of the rheumatic diseases,* 62**,** 1145-1155.

JORDAN, K., JINKS, C. & CROFT, P. 2006. A prospective study of the consulting behaviour of older people with knee pain. *Br J Gen Pract,* 56**,** 269-276.

JORDAN, K. P., EDWARDS, J. J., PORCHERET, M., HEALEY, E. L., JINKS, C., BEDSON, J., CLARKSON, K., HAY, E. M. & DZIEDZIC, K. S. 2017. Effect of a model consultation informed by guidelines on recorded quality of care of osteoarthritis (MOSAICS): a cluster randomised controlled trial in primary care. *Osteoarthritis and Cartilage,* 25**,** 1588-1597.

JPT HIGGINS, S. G. 2011. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration.

KAHAN, B. C. & JAIRATH, V. 2018. Outcome pre-specification requires sufficient detail to guard against outcome switching in clinical trials: a case study. *Trials,* 19**,** 265.

KANAVAKI, A. M., RUSHTON, A., EFSTATHIOU, N., ALRUSHUD, A., KLOCKE, R., ABHISHEK, A. & DUDA, J. L. 2017. Barriers and facilitators of physical activity in knee and hip osteoarthritis: a systematic review of qualitative evidence. *BMJ Open,* 7**,** e017042.

KAWI, J., SCHUERMAN, S., ALPERT, P. T. & YOUNG, D. 2015. *Activation to self-management and exercise in overweight and obese older women with knee osteoarthritis. [References]*, Clinical Nursing Research. Vol.24(6), 2015, pp. 644-660.

KEEFE, F. J., LEFEBVRE, J. C., EGERT, J. R., AFFLECK, G., SULLIVAN, M. J. & CALDWELL, D. S. 2000. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. *Pain,* 87**,** 325-334.

KEEFE, F. J., SOMERS, T. J. & MARTIRE, L. M. 2008. Psychologic interventions and lifestyle modifications for arthritis pain management. *Rheumatic diseases clinics of North America,* 34**,** 351-368.

KHACHIAN, A., SEYEDOSHOHADAEI, M., HAGHANI, H. & AMIRI, F. 2020. Effect of self-management program on outcome of adult knee osteoarthritis. *International Journal of Orthopaedic and Trauma Nursing,* 39**,** 100797.

KIM, C., NEVITT, M. C., NIU, J., CLANCY, M. M., LANE, N. E., LINK, T. M., VLAD, S., TOLSTYKH, I., JUNGMANN, P. M. & FELSON, D. T. 2015. Association of hip pain with radiographic evidence of hip osteoarthritis: diagnostic test study. *Bmj,* 351.

KNOOP, J., DEKKER, J., VAN DER LEEDEN, M., VAN DER ESCH, M., THORSTENSSON, C., GERRITSEN, M., VOORNEMAN, R., PETER, W., DE ROOIJ, M. & ROMVIEL, S. 2013. Knee joint stabilization therapy in patients with osteoarthritis of the knee: a randomized, controlled trial. *Osteoarthritis and cartilage,* 21**,** 1025-1034.

KOHN, M. D., SASSOON, A. A. & FERNANDO, N. D. 2016. Classifications in Brief: Kellgren-Lawrence Classification of Osteoarthritis. *Clinical orthopaedics and related research,* 474**,** 1886-1893.

LATREMOLIERE, A. & WOOLF, C. J. 2009. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *The journal of pain,* 10**,** 895-926.

LAU, E., COOPER, C., LAM, D., CHAN, V., TSANG, K. & SHAM, A. 2000. Factors associated with osteoarthritis of the hip and knee in Hong Kong Chinese: obesity, joint injury, and occupational activities. *American journal of epidemiology,* 152**,** 855-862.

LAWRENCE, J. S., BREMNER, J. M. & BIER, F. 1966. Osteo-Arthrosis: Prevalence in the Population and Relationship between Symptoms and X-ray Changes. *Annals of the Rheumatic Diseases,* 25**,** 1-24.

LEVENTHAL, H. & FRIEDMAN, M. A. 2004. Does establishing fidelity of treatment help in understanding treatment efficacy? Comment on Bellg et al.(2004).

LINS, L. & CARVALHO, F. M. 2016. SF-36 total score as a single measure of health-related quality of life: Scoping review. *SAGE Open Med,* 4**,** 2050312116671725.

LITWIC, A., EDWARDS, M., DENNISON, E. & COOPER, C. 2013. Epidemiology and Burden of Osteoarthritis. *Br Med Bull,* 105**,** 185-99.

LLUCH GIRBÉS, E., NIJS, J., TORRES-CUECO, R. & LÓPEZ CUBAS, C. 2013. Pain treatment for patients with osteoarthritis and central sensitization. *Physical therapy,* 93**,** 842-851.

MACDONALD, C. 2012. Understanding participatory action research: A qualitative research methodology option. *The Canadian Journal of Action Research,* 13**,** 34-50.

MACDONALD, W., ROGERS, A., BLAKEMAN, T. & BOWER, P. 2008. Practice nurses and the facilitation of self-management in primary care. *Journal of advanced nursing,* 62**,** 191-199.

MALFAIT, A.-M. & SCHNITZER, T. J. 2013. Towards a mechanism-based approach to pain management in osteoarthritis. *Nature Reviews Rheumatology,* 9**,** 654.

MANIAR, K. H., JONES, I. A., GOPALAKRISHNA, R. & VANGSNESS JR, C. T. 2018. Lowering side effects of NSAID usage in osteoarthritis: recent attempts at minimizing dosage. *Expert opinion on pharmacotherapy,* 19**,** 93-102.

MANN, C. & GOOBERMAN-HILL, R. 2011. Health care provision for osteoarthritis: concordance between what patients would like and what health professionals think

they should have. *Arthritis care & research,* 63**,** 963-972.

MANNINEN, P., HELIÖVAARA, M., RIIHIMÄKI, H. & SUOMALAINEN, O. 2002. Physical workload and the risk of severe knee osteoarthritis. *Scandinavian journal of work, environment & health***,** 25-32.

MARRA, C., TSUYUKI, R., SOON, J., GRUBISIC, M. & GRINDROD, K. 2010. Pharmacist-initiated Intervention Trial in Osteoarthritis (PhIT-OA). *Canadian Pharmacists Journal,* 143 (5)**,** e4.

MARRA, C. A., CIBERE, J., GRUBISIC, M., GRINDROD, K. A., GASTONGUAY, L., THOMAS, J. M., EMBLEY, P., COLLEY, L., TSUYUKI, R. T., KHAN, K. M. & ESDAILE, J. M. 2012. Pharmacist-initiated intervention trial in osteoarthritis: a multidisciplinary intervention for knee osteoarthritis. *Arthritis care & research,* 64**,** 1837-45.

MARRA, C., TSUYUKI, R., SOON, J., GRUBISIC, M. & GRINDROD, K. 2010. Pharmacist-initiated Intervention Trial in Osteoarthritis (PhIT-OA). *Canadian Pharmacists Journal,* 143 (5)**,** e4.

MARS, T., ELLARD, D., CARNES, D., HOMER, K., UNDERWOOD, M. & TAYLOR, S. J. 2013. Fidelity in complex behaviour change interventions: a standardised approach to evaluate intervention integrity. *BMJ open,* 3.

MARTEL-PELLETIER, J. 2004. Pathophysiology of osteoarthritis. *Osteoarthritis and cartilage,* 12**,** 31-33.

MARTÍNEZ-GONZÁLEZ, N. A., DJALALI, S., TANDJUNG, R., HUBER-GEISMANN, F., MARKUN, S., WENSING, M. & ROSEMANN, T. 2014. Substitution of physicians by nurses in primary care: a systematic review and meta-analysis. *BMC health services research,* 14**,** 214.

MARTÍNEZ-GONZÁLEZ, N. A., TANDJUNG, R., DJALALI, S. & ROSEMANN, T. 2015. The impact of physician–nurse task shifting in primary care on the course of disease: a systematic review. *Human resources for health,* 13**,** 55.

MASTERSON-ALGAR, P., BURTON, C. R., RYCROFT-MALONE, J., SACKLEY, C. M. & WALKER, M. F. 2014. Towards a programme theory for fidelity in the evaluation of complex interventions. *Journal of evaluation in clinical practice,* 20**,** 445-452.

MCALINDON, T., COOPER, C., KIRWAN, J. & DIEPPE, P. 1992. Knee pain and disability in the community. *Rheumatology,* 31**,** 189-192.

MCALINDON, T., COOPER, C., KIRWAN, J. & DIEPPE, P. 1993. Determinants of disability in osteoarthritis of the knee. *Annals of the rheumatic diseases,* 52**,** 258-262.

MCALINDON, T. E., FELSON, D. T., ZHANG, Y., HANNAN, M. T., ALIABADI, P., WEISSMAN, B., RUSH, D., WILSON, P. W. & JACQUES, P. 1996. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. *Annals of internal medicine,* 125**,** 353-359.

MCALINDON, T. E., WILSON, P. W., ALIABADI, P., WEISSMAN, B. & FELSON, D. T. 1999. Level of physical activity and the risk of radiographic and symptomatic knee osteoarthritis in the elderly: the Framingham study. *The American journal of medicine,* 106**,** 151-157.

MCALINDON, T. E., BANNURU, R. R., SULLIVAN, M., ARDEN, N., BERENBAUM, F., BIERMA-ZEINSTRA, S., HAWKER, G., HENROTIN, Y., HUNTER, D. & KAWAGUCHI, H. 2014. OARSI guidelines for the non-surgical management of knee osteoarthritis.

Osteoarthritis and cartilage, 22**,** 363-388.

MCHUGH, M. L. 2012. Interrater reliability: the kappa statistic. *Biochemia medica,* 22**,** 276-282.

MCKENNA, J. W., FLOWER, A. & CIULLO, S. 2014. Measuring fidelity to improve intervention effectiveness. *Intervention in School and clinic,* 50**,** 15-21.

MEASE, P. J., HANNA, S., FRAKES, E. P. & ALTMAN, R. D. 2011. Pain mechanisms in osteoarthritis: understanding the role of central pain and current approaches to its treatment. *The Journal of rheumatology,* 38**,** 1546-1551.

MECKLENBURG, G., SMITTENAAR, P., ERHART-HLEDIK, J. C., PEREZ, D. A. & HUNTER, S. 2018. Effects of a 12-week digital care program for chronic knee pain on pain, mobility, and surgery risk: randomized controlled trial. *Journal of medical Internet research,* 20**,** e9667.

MEMBERS, P. P., EXPERTS, C. S., ALBRIGHT, J., ALLMAN, R., BONFIGLIO, R. P., CONILL, A., DOBKIN, B., GUCCIONE, A. A., HASSON, S. & RUSSO, R. 2001. Philadelphia Panel Evidence–Based Clinical Practice Guidelines on Selected Rehabilitation Interventions for Knee Pain. *Physical Therapy,* 81**,** 1675-1700.

MESSIER, S. P., MIHALKO, S. L., LEGAULT, C., MILLER, G. D., NICKLAS, B. J., DEVITA, P., BEAVERS, D. P., HUNTER, D. J., LYLES, M. F., ECKSTEIN, F., WILLIAMSON, J. D., CARR, J. J., GUERMAZI, A. & LOESER, R. F. 2013. *Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: The IDEA randomized clinical trial. [References]*, JAMA: Journal of the American Medical Association. Vol.310(12), 2013, pp. 1263-1273.

METZLER, K. (ed.) 2014. *AN INTRODUCTION TO QUALITATIVE RESEARCH UWE FLICK,* Great Britain.

MICHIE, S., ATKINS, L. & WEST, R. 2014. The behaviour change wheel. *A guide to designing interventions. 1st ed. Great Britain: Silverback Publishing***,** 1003-1010.

MICHIE, S., RUMSEY, N., FUSSELL, A., HARDEMAN, W., JOHNSTON, M., NEWMAN, S. & YARDLEY, L. 2008. Improving health: changing behaviour. NHS health trainer handbook.

MICHIE, S., VAN STRALEN, M. M. & WEST, R. 2011. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implementation science,* 6**,** 42.

MILLAR, B., MCWILLIAMS, D. F., ABHISHEK, A., AKIN-AKINYOSOYE, K., AUER, D. P., CHAPMAN, V., DOHERTY, M., FERGUSON, E., GLADMAN, J. R. & GREENHAFF, P. 2020. Investigating musculoskeletal health and wellbeing; a cohort study protocol. *BMC musculoskeletal disorders,* 21**,** 1-10.

MILLER, R. E., TRAN, P. B., OBEIDAT, A. M., RAGHU, P., ISHIHARA, S., MILLER, R. J. & MALFAIT, A. M. 2015. The Role of Peripheral Nociceptive Neurons in the Pathophysiology of Osteoarthritis Pain. *Curr Osteoporos Rep,* 13**,** 318-26.

MILLS, N., METCALFE, C., RONSMANS, C., DAVIS, M., LANE, J. A., STERNE, J. A., PETERS, T. J., HAMDY, F. C., NEAL, D. E. & DONOVAN, J. L. 2006. A comparison of socio-demographic and psychological factors between patients consenting to

randomisation and those selecting treatment (the ProtecT study). *Contemporary clinical trials,* 27**,** 413-419.

MIRANDA, H., VIIKARI-JUNTURA, E., MARTIKAINEN, R. & RIIHIMÄKI, H. 2002. A prospective study on knee pain and its risk factors. *Osteoarthritis and cartilage,* 10**,** 623-630.

MONCHER, F. J. & PRINZ, R. J. 1991. Treatment fidelity in outcome studies. *Clinical psychology review,* 11**,** 247-266.

MOORE, G. F., AUDREY, S., BARKER, M., BOND, L., BONELL, C., HARDEMAN, W., MOORE, L., O'CATHAIN, A., TINATI, T. & WIGHT, D. 2015a. Process evaluation of complex interventions: Medical Research Council guidance. *bmj,* 350.

MURAD, M. H., WANG, Z., CHU, H. & LIN, L. 2019. When continuous outcomes are measured using different scales: guide for meta-analysis and interpretation. *BMJ (Clinical research ed.),* 364**,** k4817-k4817.

MURRAY, M. P., GARDNER, G. M., MOLLINGER, L. A. & SEPIC, S. B. 1980. Strength of isometric and isokinetic contractions: knee muscles of men aged 20 to 86. *Physical therapy,* 60**,** 412-419.

MUTHURI, S., MCWILLIAMS, D., DOHERTY, M. & ZHANG, W. 2011. History of knee injuries and knee osteoarthritis: a meta-analysis of observational studies. *Osteoarthritis and Cartilage,* 19**,** 1286-1293.

NELSON, A. E., ALLEN, K. D., GOLIGHTLY, Y. M., GOODE, A. P. & JORDAN, J. M. A systematic review of recommendations and guidelines for the management of osteoarthritis: the chronic osteoarthritis management initiative of the US bone and joint initiative. Seminars in arthritis and rheumatism, 2014. Elsevier, 701-712.

NEOGI, T. 2013. The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis and Cartilage,* 21**,** 1145-1153.

NEOGI, T. 2017. Structural correlates of pain in osteoarthritis. *Clin Exp Rheumatol,* 35**,** 75-78.

NEOGI, T., FELSON, D., NIU, J., NEVITT, M., LEWIS, C. E., ALIABADI, P., SACK, B., TORNER, J., BRADLEY, L. & ZHANG, Y. 2009. Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. *Bmj,* 339**,** b2844.

NICE 2014. National Institute for Health and Care Excellence. Osteoarthritis: care and management. *In:* ENGLAND, D. O. H. (ed.).

NIHR 2021. Guidance on applying for feasibility studies.

NOBLE, W. S. 2009. How does multiple testing correction work? *Nature biotechnology,* 27**,** 1135-1137.

NOMIKOS, P. A., HALL, M., FULLER, A., MILLAR, B., OGOLLAH, R., VALDES, A., DOHERTY, M., WALSH, D. A., DAS NAIR, R. & ABHISHEK, A. 2021. Fidelity assessment of nurse-led non-pharmacological package of care for knee pain in the package development phase of a feasibility randomised controlled trial based in secondary care: a mixed methods study. *BMJ Open,* 11**,** e045242.

O'CATHAIN, A., CROOT, L., DUNCAN, E., ROUSSEAU, N., SWORN, K., TURNER, K. M., YARDLEY, L. & HODDINOTT, P. 2019. Guidance on how to develop complex interventions to improve health and healthcare. *BMJ open,* 9**,** e029954.

O'REILLY, S. C., MUIR, K. R. & DOHERTY, M. 1996. Screening for pain in knee osteoarthritis: which question? *Annals of the rheumatic diseases,* 55**,** 931-933.

OAKLEY, A., STRANGE, V., BONELL, C., ALLEN, E. & STEPHENSON, J. 2006. Process evaluation in randomised controlled trials of complex interventions. *Bmj,* 332**,** 413-416.

ODDING, E., VALKENBURG, H. A., ALGRA, D., VANDENOUWELAND, F. A., GROBBEE, D. E. & HOFMAN, A. 1998. Associations of radiological osteoarthritis of the hip and knee with locomotor disability in the Rotterdam Study. *Annals of the rheumatic diseases,* 57**,** 203-208.

OGRINC, G., DAVIES, L., GOODMAN, D., BATALDEN, P., DAVIDOFF, F. & STEVENS, D. 2016. SQUIRE 2.0 (Standards for QUality Improvement Reporting Excellence): revised publication guidelines from a detailed consensus process. *BMJ Qual Saf,* 25**,** 986-992.

ORGANIZATION, W. H. 2007. Task shifting: rational redistribution of tasks among health workforce teams: global recommendations and guidelines.

PALMER, S., DOMAILLE, M., CRAMP, F. & JOHNSON, M. I. 2010. *Rheumatology,* 1)**,** i33-i34.

PALMER, S., DOMAILLE, M., CRAMP, F., WALSH, N., POLLOCK, J., KIRWAN, J. & JOHNSON, M. I. 2014. Transcutaneous electrical nerve stimulation as an adjunct to education and exercise for knee osteoarthritis: a randomized controlled trial. *Arthritis care & research,* 66**,** 387-94.

PARRY, R., PINO, M., FAULL, C. & FEATHERS, L. 2016. Acceptability and design of video-based research on healthcare communication: evidence and recommendations. *Patient education and counseling,* 99**,** 1271-1284.

PASKINS, Z., SANDERS, T. & HASSELL, A. B. 2014. Comparison of patient experiences of the osteoarthritis consultation with GP attitudes and beliefs to OA: a narrative review. *BMC family practice,* 15**,** 1-10.

PATEL, A., BUSZEWICZ, M., BEECHAM, J., GRIFFIN, M., RAIT, G., NAZARETH, I., ATKINSON, A., BARLOW, J. & HAINES, A. 2009. Economic evaluation of arthritis self management in primary care. *BMJ,* 339**,** b3532.

PEAT, G., MCCARNEY, R. & CROFT, P. 2001. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Annals of the rheumatic diseases,* 60**,** 91-97.

PENDLETON, A., ARDEN, N., DOUGADOS, M., DOHERTY, M., BANNWARTH, B.,

BIJLSMA, J. W. J., CLUZEAU, F., COOPER, C., DIEPPE, P. A., GÜNTHER, K.-P., HAUSELMANN, H. J., HERRERO-BEAUMONT, G., KAKLAMANIS, P. M., LEEB, B., LEQUESNE, M., LOHMANDER, S., MAZIERES, B., MOLA, E.-M., PAVELKA, K., SERNI, U., SWOBODA, B., VERBRUGGEN, A. A., WESELOH, G. & ZIMMERMANN-GORSKA, I. 2000. EULAR recommendations for the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Annals of the Rheumatic Diseases,* 59**,** 936-944.

PETERS, J. L., SUTTON, A. J., JONES, D. R., ABRAMS, K. R. & RUSHTON, L. 2006.

Comparison of Two Methods to Detect Publication Bias in Meta-analysis. *JAMA,* 295**,** 676-680.

PETTICREW, M. 2011. When are complex interventions 'complex'? When are simple interventions 'simple'? *European Journal of Public Health,* 21**,** 397-398.

POLTAWSKI, L., NORRIS, M. & DEAN, S. 2014. Intervention fidelity: developing an experience-based model for rehabilitation research. *Journal of rehabilitation medicine,* 46**,** 609-615.

POLYKARPOS ANGELOS NOMIKOS, M. H., ROSHAN DAS NAIR, ABHISHEK ABHISHEK. 2020. A systematic review and meta-analysis of complex packages of care for knee osteoarthritis (OA) and knee pain study protocol. 7 September 2020 ed.

POPE, C., ZIEDLAND, S. & MAYS, N. 2000. Qualitative research in health care: Analysing qualitative data. 320.

PORCHERET, M., JORDAN, K., JINKS, C. & SOCIETY, P. C. I. C. W. T. P. C. R. 2007. Primary care treatment of knee pain—a survey in older adults. *Rheumatology,* 46**,** 1694-1700.

RADFORD, K., SUTTON, C. J., SACH, T., HOLMES, J., WATKINS, C. L., FORSHAW, D., JONES, T., HOFFMAN, K., O'CONNOR, R. & TYERMAN, R. 2018. Early, specialist vocational rehabilitation to facilitate return to work after traumatic brain injury: the FRESH feasibility RCT. *Health technology assessment,* 22**,** 1-156.

RAVAUD, P., FLIPO, R. M., BOUTRON, I., ROY, C., MAHMOUDI, A., GIRAUDEAU, B. & PHAM, T. 2009. ARTIST (osteoarthritis intervention standardized) study of standardised consultation versus usual care for patients with osteoarthritis of the knee in primary care in France: pragmatic randomised controlled trial. *BMJ,* 338**,** b421.

REGISTRY, N. J. 2015. Public and patient guide to the NJR's 12th annual report Knee replacement ed.

RELTON, C., TORGERSON, D., O'CATHAIN, A. & NICHOLL, J. 2010. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design. *Bmj,* 340**,** c1066.

REZENDE, M. U., FRUCCHI, R., PAILO, A. F., CAMPOS, G. C., PASQUALIN, T. & HISSADOMI, M. I. 2017. Parqve: Project Arthritis Recovering Quality of Life through Education: Two-Year Results. *Acta Ortopedica Brasileira,* 25**,** 18-24.

RICHARD, J., PILLEMER, D. B. & LIGHT, R. J. 2009. *Summing up: the science of reviewing research*, Harvard University Press.

RITCHIE, J., LEWIS, J., NICHOLLS, C. M. & ORMSTON, R. 2013. *Qualitative research practice: A guide for social science students and researchers*, sage.

RITCHIE, J., SPENCER, L. & O'CONNOR, W. 2003. Carrying out qualitative analysis. *Qualitative research practice: A guide for social science students and researchers,* 2003**,** 219-62.

RM, F., RT, T., JA, D. & RS, G. 2019. Non-pharmacological and non-surgical interventions for knee osteoarthritis: a systematic review and meta-analysis. *Acta reumatologica portuguesa,* 44.

ROBBINS, S. R., MELO, L. R. S., URBAN, H., DEVEZA, L. A., ASHER, R., JOHNSON, V. L.

& HUNTER, D. J. 2020. Is a stepped-care intervention effective in overweight and obese people with medial tibiofemoral osteoarthritis? The STrEAMline study: A randomised controlled trial. *Arthritis care & research.,* 21.

RØGIND, H., BIBOW-NIELSEN, B., JENSEN, B., MØLLER, H. C., FRIMODT-MØLLER, H. & BLIDDAL, H. 1998. The effects of a physical training program on patients with osteoarthritis of the knees. *Archives of physical medicine and rehabilitation,* 79**,** 1421-1427.

ROOS, E. M. 2005. Joint injury causes knee osteoarthritis in young adults. *Current opinion in rheumatology,* 17**,** 195-200.

ROOS, E. M. & LOHMANDER, L. S. 2003. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health and quality of life outcomes,* 1**,** 64-64.

ROWE, G., LAMBERT, N., BOWLING, A., EBRAHIM, S., WAKELING, I. & THOMSON, R. 2005. Assessing patients' preferences for treatments for angina using a modified repertory grid method. *Social science & medicine,* 60**,** 2585-2595.

SAFFI, M. A. L., POLANCZYK, C. A. & RABELO-SILVA, E. R. 2014. Lifestyle interventions reduce cardiovascular risk in patients with coronary artery disease: A randomized clinical trial. *European Journal of Cardiovascular Nursing,* 13**,** 436-443.

SAKALAUSKIENĖ, G. & JAUNIŠKIENĖ, D. 2010. Osteoarthritis: etiology, epidemiology, impact on the individual and society and the main principles of management. *Medicina,* 46**,** 790.

SANDERS, C., DONOVAN, J. & DIEPPE, P. 2004. Unmet need for joint replacement: a qualitative investigation of barriers to treatment among individuals with severe pain and disability of the hip and knee. *Rheumatology,* 43**,** 353-357.

SARABOON, Y., AREE-UE, S. & MARUO, S. J. 2015. The effect of multifactorial intervention programs on health behavior and symptom control among community-dwelling overweight older adults with knee osteoarthritis. *Orthopaedic Nursing,* 34**,** 296-308.

SARMANOVA, A., HALL, M., FERNANDES, G. S., BHATTACHARYA, A., VALDES, A. M., WALSH, D. A., DOHERTY, M. & ZHANG, W. 2017. Association between ultrasound-detected synovitis and knee pain: a population-based case–control study with both cross-sectional and follow-up data. *Arthritis research & therapy,* 19**,** 1-9.

SCHAIBLE, H.-G. & GRUBB, B. D. 1993. Afferent and spinal mechanisms of joint pain. *Pain,* 55**,** 5-54.

SCHIPHOF, D., BOERS, M. & BIERMA-ZEINSTRA, S. M. A. 2008. Differences in descriptions of Kellgren and Lawrence grades of knee osteoarthritis. *Annals of the Rheumatic Diseases,* 67**,** 1034-1036.

SCHOUTEN, J., VAN DEN OUWELAND, F. & VALKENBURG, H. 1992. A 12 year follow up study in the general population on prognostic factors of cartilage loss in osteoarthritis of the knee. *Annals of the rheumatic diseases,* 51**,** 932-937.

SCHULTE, A. C., EASTON, J. E. & PARKER, J. 2009. Advances in treatment integrity research: Multidisciplinary perspectives on the conceptualization, measurement, and enhancement of treatment integrity. *School Psychology Review,* 38.

SCHULZ, K. F., ALTMAN, D. G. & MOHER, D. 2010. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Annals of internal medicine,* 152**,** 726-732.

SCHULZ, K. F., CHALMERS, I., HAYES, R. J. & ALTMAN, D. G. 1995. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Jama,* 273**,** 408-412.

SEKHON, M., CARTWRIGHT, M. & FRANCIS, J. J. 2017. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. *BMC health services research,* 17**,** 1-13.

SHARMA, L., CAHUE, S., SONG, J., HAYES, K., PAI, Y. C. & DUNLOP, D. 2003a. Physical functioning over three years in knee osteoarthritis: role of psychosocial, local mechanical, and neuromuscular factors. *Arthritis & Rheumatism,* 48**,** 3359-3370.

SHARMA, L., DUNLOP, D. D., CAHUE, S., SONG, J. & HAYES, K. W. 2003b. Quadriceps strength and osteoarthritis progression in malaligned and lax knees. *Annals of internal medicine,* 138**,** 613-619.

SHARMA, L., SONG, J., FELSON, D. T., CAHUE, S., SHAMIYEH, E. & DUNLOP, D. D. 2001. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. *Jama,* 286**,** 188-195.

SHEKELLE, P. G., WOOLF, S. H., ECCLES, M. & GRIMSHAW, J. 1999. Developing guidelines. *BMJ,* 318**,** 593-596.

SHUM, C., HUMPHREYS, A., WHEELER, D., COCHRANE, M.-A., SKODA, S. & CLEMENT, S. 2000. Nurse management of patients with minor illnesses in general practice: multicentre, randomised controlled trial. *BMJ,* 320**,** 1038-1043.

SINUSAS, K. 2012. Osteoarthritis: diagnosis and treatment. *American family physician,* 85**,** 49-56.

SISK, J. E., HEBERT, P. L., HOROWITZ, C. R., MCLAUGHLIN, M. A., WANG, J. J. & CHASSIN, M. R. 2006. Effects of nurse management on the quality of heart failure care in minority communities: a randomized trial. *Annals of internal medicine,* 145**,** 273-283.

SKOU, S. T. & ROOS, E. M. 2017. Good Life with osteoArthritis in Denmark (GLA: D™): evidence-based education and supervised neuromuscular exercise delivered by certified physiotherapists nationwide. *BMC musculoskeletal disorders,* 18**,** 1-13.

SMIDT, N., DE VET, H. C. W., BOUTER, L. M. & DEKKER, J. 2005. Effectiveness of exercise therapy: A best-evidence summary of systematic reviews. *Australian Journal of Physiotherapy,* 51**,** 71-85.

SMITH, J. & FIRTH, J. 2011. Qualitative data analysis: the framework approach. *Nurse researcher,* 18**,** 52-62.

SOWERS, M., KARVONEN-GUTIERREZ, C. A., JACOBSON, J. A., JIANG, Y. & YOSEF, M. 2011. Associations of anatomical measures from MRI with radiographically defined knee osteoarthritis score, pain, and physical functioning. *The Journal of Bone and Joint Surgery. American volume.,* 93**,** 241.

SOWERS, M. R., MCCONNELL, D., JANNAUSCH, M., BUYUKTUR, A. G., HOCHBERG, M.

& JAMADAR, D. A. 2006. Estradiol and its metabolites and their association with knee osteoarthritis. *Arthritis & Rheumatology,* 54**,** 2481-2487.

SPECTOR, T., HART, D., BYRNE, J., HARRIS, P., DACRE, J. & DOYLE, D. 1993. Definition of osteoarthritis of the knee for epidemiological studies. *Annals of the rheumatic diseases,* 52**,** 790.

SPECTOR, T. D., CICUTTINI, F., BAKER, J., LOUGHLIN, J. & HART, D. 1996. Genetic influences on osteoarthritis in women: a twin study. *Bmj,* 312**,** 940-943.

SPENCER, L. & RITCHIE, J. 2002. Qualitative data analysis for applied policy research. *Analyzing qualitative data.* Routledge.

SRIVASTAVA, A. & THOMSON, S. B. 2009. Framework analysis: a qualitative methodology for applied policy research.

STERNE, J. A., SAVOVIĆ, J., PAGE, M. J., ELBERS, R. G., BLENCOWE, N. S., BOUTRON, I., CATES, C. J., CHENG, H.-Y., CORBETT, M. S. & ELDRIDGE, S. M. 2019. RoB 2: a revised tool for assessing risk of bias in randomised trials. *bmj,* 366.

STERNE, J. A., SUTTON, A. J., IOANNIDIS, J. P., TERRIN, N., JONES, D. R., LAU, J., CARPENTER, J., RÜCKER, G., HARBORD, R. M. & SCHMID, C. H. 2011. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *Bmj,* 343.

STRÖMBERG, A., MÅRTENSSON, J., FRIDLUND, B., LEVIN, L.-Å., KARLSSON, J.-E. & DAHLSTRÖM, U. 2003. Nurse-led heart failure clinics improve survival and self-care behaviour in patients with heart failure: results from a prospective, randomised trial. *European heart journal,* 24**,** 1014-1023.

SUN, X., IOANNIDIS, J. P., AGORITSAS, T., ALBA, A. C. & GUYATT, G. 2014. How to use a subgroup analysis: users' guide to the medical literature. *Jama,* 311**,** 405-411.

SURI, S., GILL, S. E., DE CAMIN, S. M., MCWILLIAMS, D. F., WILSON, D. & WALSH, D. A. 2007. Neurovascular invasion at the osteochondral junction and in osteophytes in osteoarthritis. *Annals of the rheumatic diseases,* 66**,** 1423-1428.

SWINDLE, T., SELIG, J. P., RUTLEDGE, J. M., WHITESIDE-MANSELL, L. & CURRAN, G. 2018. Fidelity monitoring in complex interventions: a case study of the WISE intervention. *Archives of Public Health,* 76**,** 53.

TAGLIETTI, M., FACCI, L. M., TRELHA, C. S., DE MELO, F. C., DA SILVA, D. W., SAWCZUK, G., RUIVO, T. M., DE SOUZA, T. B., SFORZA, C. & CARDOSO, J. R. 2018. *Effectiveness of aquatic exercises compared to patient-education on health status in individuals with knee osteoarthritis: A randomized controlled trial. [References]*, Clinical Rehabilitation. Vol.32(6), 2018, pp. 766-776.

TAN, B. Y., DING, B. T. K., PEREIRA, M. J., SKOU, S. T., THUMBOO, J. & CAR, J. 2020. Collaborative Model of Care between Orthopaedics and Allied Healthcare Professionals Trial (CONNACT)–A Feasibility Study in patients with knee osteoarthritis using a mixed method approach. *BMC Musculoskeletal Disorders,* 21**,** 1-14.

TEO, P. L., BENNELL, K. L., LAWFORD, B., EGERTON, T., DZIEDZIC, K. & HINMAN, R. S. 2021. Patient experiences with physiotherapy for knee osteoarthritis in Australia—a qualitative study. *BMJ Open,* 11**,** e043689.

THOMAS, D. R. 2006. A General Inductive Approach for Analyzing Qualitative Evaluation Data. *American Journal of Evaluation,* 27**,** 237-246.

THORSTENSSON, C. A., ANDERSSON, M., JÖNSSON, H., SAXNE, T. & PETERSSON, I. 2009. Natural course of knee osteoarthritis in middle-aged subjects with knee pain: 12-year follow-up using clinical and radiographic criteria. *Annals of the rheumatic diseases,* 68**,** 1890-1893.

THORSTENSSON, C. A., GARELLICK, G., RYSTEDT, H. & DAHLBERG, L. E. 2015. Better management of patients with osteoarthritis: development and nationwide implementation of an evidence-based supported osteoarthritis self-management programme. *Musculoskeletal care,* 13**,** 67-75.

THYRIAN, J. R., FREYER-ADAM, J., HANNÖVER, W., RÖSKE, K., MENTZEL, F., KUFELD, C., BISCHOF, G., RUMPF, H.-J., JOHN, U. & HAPKE, U. 2010. Population-based smoking cessation in women post partum: adherence to motivational interviewing in relation to client characteristics and behavioural outcomes. *Midwifery,* 26**,** 202-210.

TICKLE-DEGNEN, L. 2013. Nuts and Bolts of Conducting Feasibility Studies. *The American Journal of Occupational Therapy,* 67**,** 171-176.

TONG, A., SAINSBURY, P. & CRAIG, J. 2007. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International journal for quality in health care,* 19**,** 349-357.

TOOMEY, E., MATTHEWS, J., GUERIN, S. & HURLEY, D. A. 2016. Development of a Feasible Implementation Fidelity Protocol Within a Complex Physical Therapy–Led Self-Management Intervention. *Physical Therapy,* 96**,** 1287-1298.

TOOMEY, E., MATTHEWS, J. & HURLEY, D. A. 2017. Using mixed methods to assess fidelity of delivery and its influencing factors in a complex self-management intervention for people with osteoarthritis and low back pain. *BMJ open,* 7**,** e015452.

TORGERSON, D. & SIBBALD, B. 1998. Understanding controlled trials: What is a patient preference trial? *BMJ,* 316**,** 360.

TURNER, A. P., BARLOW, J. H., BUSZEWICZ, M., ATKINSON, A. & RAIT, G. 2007. Beliefs about the causes of osteoarthritis among primary care patients. *Arthritis care & research,* 57**,** 267-271.

VICTOR, C. R., ROSS, F. & AXFORD, J. 2004. Capturing lay perspectives in a randomized control trial of a health promotion intervention for people with osteoarthritis of the knee. *Journal of evaluation in clinical practice,* 10**,** 63-70.

VOGELS, E., HENDRIKS, H., VAN BAAR, M., DEKKER, J., HOPMAN-ROCK, M., OOSTENDORP, R., HULLEGIE, W., BLOO, H., HILBERDINK, W. & MUNNEKE, M. 2001. Clinical practice guidelines for physical therapy in patients with osteoarthritis of the hip or knee. *Amersfoort: KNGF*.

WAGLAND, R., ELLIS, J., BAILEY, C. D., HAINES, J., CARESS, A., WILLIAMS, M. L., LORIGAN, P., SMITH, J., TISHELMAN, C. & BOOTON, R. 2012. Considerations in developing and delivering a non-pharmacological intervention for symptom management in lung cancer: the views of health care professionals. *Supportive Care in Cancer,* 20**,** 2565-2574.

WAGNER, E. H. 1998. Chronic disease management: what will it take to improve care for chronic illness? *Effective clinical practice: ECP,* 1**,** 2.

WALKER, M. F., HOFFMANN, T. C., BRADY, M. C., DEAN, C. M., ENG, J. J., FARRIN, A. J., FELIX, C., FORSTER, A., LANGHORNE, P. & LYNCH, E. A. 2017. Improving the development, monitoring and reporting of stroke rehabilitation research: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. *International Journal of Stroke,* 12**,** 472-479.

WALLER, B., OGONOWSKA-SLODOWNIK, A., VITOR, M., LAMBECK, J., DALY, D., KUJALA, U. M. & HEINONEN, A. 2014. Effect of Therapeutic Aquatic Exercise on Symptoms and Function Associated With Lower Limb Osteoarthritis: Systematic Review With Meta-Analysis. *Physical Therapy,* 94**,** 1383-1395.

WALTON, H. 2018. *Evaluating the implementation of interventions to improve indepedence in dementia* Doctor of Philosophy, University College London.

WALTON, H., SPECTOR, A., ROBERTS, A., WILLIAMSON, M., BHATT, J., TOMBOR, I. & MICHIE, S. 2020. Developing strategies to improve fidelity of delivery of, and engagement with, a complex intervention to improve independence in dementia: a mixed methods study. *BMC Medical Research Methodology,* 20**,** 1-19.

WANG, S. Y., OLSON-KELLOGG, B., SHAMLIYAN, T. A., CHOI, J. Y., RAMAKRISHNAN, R., & KANE, R. L. (2012). Physical therapy interventions for knee pain secondary to osteoarthritis: a systematic review. *Annals of internal medicine*, *157*(9), 632-644.

WANG, B., STANTON, B., DEVEAUX, L., POITIER, M., LUNN, S., KOCI, V., ADDERLEY, R., KALJEE, L., MARSHALL, S. & LI, X. 2015. Factors influencing implementation dose and fidelity thereof and related student outcomes of an evidence-based national HIV prevention program. *Implementation science,* 10**,** 1-13.

WELCH, G., GARB, J., ZAGARINS, S., LENDEL, I. & GABBAY, R. A. 2010. Nurse diabetes case management interventions and blood glucose control: Results of a meta-analysis. *Diabetes Research and Clinical Practice,* 88**,** 1-6.

WHITE, A., FOSTER, N. E., CUMMINGS, M., & BARLAS, P. (2007). Acupuncture treatment for chronic knee pain: a systematic review. *Rheumatology*, *46*(3), 384-390.

WILKIE, R., PEAT, G., THOMAS, E. & CROFT, P. 2007. Factors associated with restricted mobility outside the home in community-dwelling adults ages fifty years and older with knee pain: An example of use of the International Classification of Functioning to investigate participation restriction. *Arthritis Care & Research,* 57**,** 1381-1389.

WILLIAMS, S. L., MCSHARRY, J., TAYLOR, C., DALE, J., MICHIE, S. & FRENCH, D. P. 2020. Translating a walking intervention for health professional delivery within primary care: A mixed-methods treatment fidelity assessment. *British Journal of Health Psychology,* 25**,** 17-38.

WOOLF, C. J. 2004. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Annals of internal medicine,* 140**,** 441-451.

YAMATO, T. P., MAHER, C. G., SARAGIOTTO, B. T., CATLEY, M. J. & MOSELEY, A. M. 2018. Rasch analysis suggested that items from the template for intervention description and replication (TIDieR) checklist can be summed to create a score. *Journal of clinical epidemiology,* 101**,** 28-34.

YAMATO, T. P., MAHER, C. G., SARAGIOTTO, B. T., HOFFMANN, T. C. & MOSELEY, A. M. 2016. How completely are physiotherapy interventions described in reports of randomised trials? *Physiotherapy,* 102**,** 121-126.

YIP, Y. B., SIT, J. W., WONG, D. Y., CHONG, S. Y. & CHUNG, L. H. 2008. A 1-year follow-up of an experimental study of a self-management arthritis programme with an added exercise component of clients with osteoarthritis of the knee. *Psychology Health & Medicine,* 13**,** 402-14.

YOSHIMURA, N., NISHIOKA, S., KINOSHITA, H., HORI, N., NISHIOKA, T., RYUJIN, M., MANTANI, Y., MIYAKE, M., COGGON, D. & COOPER, C. 2004. Risk factors for knee osteoarthritis in Japanese women: heavy weight, previous joint injuries, and occupational activities. *The Journal of rheumatology,* 31**,** 157-162.

YUSUF, E., KORTEKAAS, M. C., WATT, I., HUIZINGA, T. W. & KLOPPENBURG, M. 2011. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. *Annals of the rheumatic diseases,* 70**,** 60-67.

ZHANG, W., DOHERTY, M., PEAT, G., BIERMA-ZEINSTRA, M., ARDEN, N., BRESNIHAN, B., HERRERO-BEAUMONT, G., KIRSCHNER, S., LEEB, B. & LOHMANDER, L. 2010a. EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. *Annals of the rheumatic diseases,* 69**,** 483-489.

ZHANG, W., MOSKOWITZ, R., NUKI, G., ABRAMSON, S., ALTMAN, R., ARDEN, N., BIERMA-ZEINSTRA, S., BRANDT, K., CROFT, P. & DOHERTY, M. 2007. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis and cartilage,* 15**,** 981-1000.

ZHANG, W., MOSKOWITZ, R., NUKI, G., ABRAMSON, S., ALTMAN, R., ARDEN, N., BIERMA-ZEINSTRA, S., BRANDT, K., CROFT, P. & DOHERTY, M. 2008. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis and cartilage,* 16**,** 137-162.

ZHANG, W., NUKI, G., MOSKOWITZ, R., ABRAMSON, S., ALTMAN, R., ARDEN, N., BIERMA-ZEINSTRA, S., BRANDT, K., CROFT, P. & DOHERTY, M. 2010b. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis and cartilage,* 18**,** 476-499.

ZHANG, Y., HANNAN, M., CHAISSON, C., MCALINDON, T., EVANS, S., ALIABADI, P., LEVY, D. & FELSON, D. 2000. Bone mineral density and risk of incident and progressive radiographic knee osteoarthritis in women: the Framingham Study. *The Journal of rheumatology,* 27**,** 1032-1037.

ZHANG, Y., NEVITT, M., NIU, J., LEWIS, C., TORNER, J., GUERMAZI, A., ROEMER, F., MCCULLOCH, C. & FELSON, D. T. 2011. Fluctuation of knee pain and changes in bone marrow lesions, effusions, and synovitis on magnetic resonance imaging. *Arthritis & Rheumatism,* 63**,** 691-699.

Appendix I Patient Advisory Group

Patients:

PPI-1 – Stapleford exercise package

Has injections for pain in hips instead of replacements, but won't have replacements as wants to play badminton.

Is in walking group. Went for physio when had knee pain some years ago – went for 6 weeks then had 6 weeks of discussion afterwards, group based package, found it was useful.

PPI-2

Doesn't know if she has OA. Terribly swollen knees (double size), 3 long scars.

Walks to & from daughter's (1 mile each way), does gardening, very active. Knees very bad at times, no experience of physio. Philosophy is "got to keep going".

PPI-3

Got OA in knees, worked with Jane Flewitt. Been on RCT drug trial, had X-ray for knees. Years ago went for some physio in Stapleford, good if this was somewhere else for ease of access. Yesterday everything hurt but didn't know which part hurt most. Has handrails in house & step outside front door, balance not good. Need to think of health & safety and to keep yourself safe.

Got knee pain, had appendix out 1 month ago, 74 years old.

Three very different experiences of exercise.

MH – very different experiences of care in primary care, some get loads, some get very little. Not everyone can get access to physio so we want to train up nurses in primary care to do tailored exercise, so rather than people having to wait 3 months to get physio

referral.

The Concept: Give nurses info about OA, & train them to give people exercises. 2 parts to NICE:

1) Aerobic exercise (get heart rate going), up to half an hour a day (can do it in 10 minutes sessions). Train nurses to discuss patients' preferences so can signpost patients (eg walking for health groups, exercise groups).
2) Muscle strengthening, muscles around knee/hip. Weak quadriceps (people with knee OA), so nurses will be trained in how to do this option
    a. Could have booklet of work exercises
    b. Or worksheets

Exercises are on a case by case basis for OA. Also need to wear appropriate footwear, measure up for stick. Use hot/cold to manage pain.

Education element: looking at exercise, advise signpost to weight loss services for obesity. Obesity aggravates pain. GPs limited with time for patients, nurses would have time to explore these issues more. Can gage patients understanding, explore beliefs and perceptions, address misbeliefs. People can manage without surgery or don't want it.

MH- Question: is there anything else you can think of that needs to be included?

People have to do it for themselves, you can get leaflets but you have to help yourself.

MH – Adherence. Get these people to score (can't do it, too lazy to do it), so can problem solve this, maybe make it social, make it a habit. Walking poles can help (don't look like old-fashioned stick, helps with safety & confidence going down slopes).

MH- Would you mind nurses asking you about adherence?

Yes if it was too often.

MH- Second part of adherence: Booklets, sheets to record activity.

PPI-2 – filled in diary for 2 years about activity & 3 month phone calls.

PPI-1- Forgetful so go up & down stairs

MH – Anything else for package?

PPI-1– doing it as a group is helpful as it is easier in a group.

MH – signposts good.

PPI-1– you get people fall by wayside as they don't keep up with the exercises.

MH – package will be delivered by 6 face to face visits over 12 weeks. Weekly visits too much if you do other things, but might help get someone started. Getting out is an incentive, communication and talking with other people.

MH- NICE recommends exercise first & pharmacological second, so we are to say whether exercise should come first or drugs.

MH – thought about order of treatment (?)

PPI-1, PPI-2 and PPI-3 – would prefer exercise first, putting drugs first is like putting "cart before horse". You would need to see how you were and then you might not need so much.

MH – getting the drugs first means getting on top of pain, and then more likely to do exercise. Would doing drugs first put people off?

All wanted to do exercise first.

MH - Test package with small group first, so nurses are confidant and competent. Will audio record nurse and interviews with patients. Next stage will be to see if order make a difference, this would feed to larger trial, nurse just does this for this trial. Also looking at current medication.

This is a lot to ask of people at a first visit, would be 2-3 hours: follow up visits would be quite quick.

PPI-2– fell before Christmas and couldn't get back up.

MH – also doing interviews to see how people get on with exercise package. People will be recruited from cohort but for main trial it will be from GP surgeries. 3rd group – normal care. Don't make it too daunting.

Diary entry: Having to score items on scale Level 1 – 10 is daunting and frustrating.

Prefer options with words. Can tick most appropriate option and a have a final option of "other" where they can enter free text if necessary.

Could offer phone sessions instead of face to face.

Difficulties – if not used to exercise that might put people off. Some people like quick fixes, easy option. It is all about attitude. Lots of people just sit there, don't want to do anything.

Making sure when we advertise that it is tailored package, not going to signpost wheelchair user to a walking group.

Filling in diary booklet/ weekly sheets when you are on your own twice a day – too much. Once a day in evening is enough on your own. You have to do everything yourself so don't always have time to do all visits and diary filling; but person on own would like to come in to socialise.

a) Weekly sheet to stick to fridge with magnet so you can tick in evening.

b) At night seem more likely to do it.

Give people option, choice of options of formats (diary format, calendar format).

MH - is it ethical to split the treatments into that sort of order (exercise then drugs, vice versa? Changing order.

Maybe have music to go with exercises, exercise and diet advice. Do you want to give all exercises in booklets, or in weekly sheets so can build up. Maybe doing fewer exercises and more of them.

Folders and sheets every week, and then see progression. Sections for advice, diet and exercises, don't want folders to be too big or clumsy.

Customised booklet: Folder with plastic pockets- build up exercise sheets, local information about groups/ opportunities each week

Appendix II Search strategy (Medline)

1. exp osteoarthritis/

2. Osteoarth*.mp.

3. Arthrosis.mp. or Osteoarthritis/

4. (degenerative adj2 arthritis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

5. 1 or 2 or 3 or 4

6. Knee/

7. exp knee Joint/

8. Knee*.tw.

9. 6 or 7 or 8

10. 5 and 9

11. knee pain.mp.

12. persistent knee pain.mp.

13. Chronic knee pain.mp.

14. 11 or 12 or 13

15. 10 or 14

16. exp physical activity/

17. (Physical* adj2 (activity or training or therapy*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

18. (Exercis* or rehabilitation* or treatment*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

19. ((Closed kinetic chain* or open kinetic chain* or isokinetic* or isometric* or anaerobic* or muscle* or stretching* or aerobic* or isotonic* or treadmill*or endurance* or walking*) adj1 exercise*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

20. swimming.mp.

21. (Running or jogging).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

22. physiotherap*.mp.

23. exercise based rehabilitation.mp.

24. integrated rehabilitation.mp.

25. Flexibility exercise.mp.

26. Resistance training.mp. or Resistance Training/

27. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28. Healthy Behavior/ or healthy lifestyle.mp. or Healthy Lifestyle/

29. Dietary restriction.mp.

30. Meal replacement.mp.

31. (Diet adj2 (therapy* or treatment*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

32. ((Low carbohydrate* or low calor* or low fat* or vegetarian*) adj1 diet*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

33. Energy intake/ or adipos*/ or Body Mass Index/ or Overweight/

34. exp Weight loss/ or weight loss.mp. or intentional weight loss.mp.

35. Caloric Restriction/ or Obesity/ or Body Weight/ or hypo.mp. or hypocloric diet/ [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

36. exp Obesity/ or obesity.mp.

37. ((Low carbohydrate* or low calor* or low fat* or vegetarian*) adj1 diet*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

38. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37

39. 27 and 38

40. Randomized Controlled Trials as Topic/ or Random* Control Trial.mp. or Clinical Trials as Topic/

41. Clinical Trials.mp. or exp Clinical Trial/

42. exp Randomized Controlled Trial/ or Clinical Trial/ or Trials.mp.

43. randomized.ab.

44. trial.mp.

45. 40 or 41 or 42 or 43 or 44

46. 15 and 39

47. Self-management.mp. or exp Self-Management/

48. Patient education.mp. or exp patient education/

49. Educational programs.mp. or exp educational programs/

50. Self-care.mp. or exp self care/

51. 47 or 48 or 49 or 50

52. 15 and 51

53. 45 and 52

54. 45 and 46

55. 53 or 54

Appendix III Data extraction form

Date form started:

Date form completed:

Name of review author completing this form:

Section A. Study's information

1. Geographic location *(country where the study was completed):*

2. Setting *(primary care, secondary care, community):*

3. Aim of the study *(what was the trial designed to assess):*

4. Study design *(e.g. parallel, factorial, cross over, cluster):*

5. Was the study single centre or Multicentre ?

6. Funding source *(details about possible or explicit conflicts of inerest):*

7. Informed consent obtained ? ***Yes*** ☐ ***No*** ☐ ***Unclear*** ☐

8. Ethical Approval obtained? ***Yes*** ☐ ***No*** ☐ ***Unclear*** ☐

9. Is the eligibility criteria for the study comprehensively described? ***Yes*** ☐ ***No*** ☐

a. *Which diagnostic criteria for knee osteoarthritis was used:*

- **Kellgren & Lawrence classification system** (more than equal to grade 2) ☐
- ***ACR criteria for knee osteoarthritis*** ☐
- ***Knee pain on most days of the previous month*** ☐
- ***Physician or doctor diagnosed knee OA*** ☐
- ***Other (please specify below)*** ☐

If criteria is adequately described and consists of any of the first four aforementioned proceed to* ***number 10.*

10. Number of Arms or groups *(including control groups –briefly describe each):*

11. Number and specific components of the intervention on each arm *(detail description):*

Details of the Study	*Group A (active)*	*Group B (active)*	*Group C (active)*
Individualised or group			
Number of sessions			
Length of time (session)			
Length of Programme			

12. Intervention description:

A. Types of exercises used:

	Yes	***No***
Aerobic	☐	☐
Anaerobic	☐	☐
Mixed	☐	☐
Flexibility	☐	☐

Other (please specify): _____

Please refer to the box below for more information:

Aerobic (Running, cycling, swimming, brisk walking, skipping rope, rowing, hiking, dancing, playing tennis, continuous training, and long distance running), **Anaerobic** (strength and resistance training, weight training, functional training, eccentric training, interval training, sprinting, and high-intensity interval training), **Mixed**, **flexibility** (Stretching). **Mind-Body exercise**

B. Types of weight loss strategies used: ***Weight loss surgery***

	Yes	***No***
Physical activity for weight loss	☐	☐
Dietary management	☐	☐
Support systems involved	☐	☐
Behaviour and lifestyle modification	☐	☐
Prescription of drugs	☐	☐
OTC	☐	☐
Supplements	☐	☐

Other (please specify): _____

Please refer to the box below for more information:

Weight loss surgery: also called bariatric or metabolic surgery, is used as a treatment for people who are very obese (BMI of 40 or more). Weight loss surgery consists of gastric band, gastric bypass, and sleeve gastrectomy. **Dietary management** and **dietary restriction** refers to nutritionally balanced hypocaloric diet, meal replacements, high-protein with low-carbohydrate diet, low-fat diets, high-fiber diets, very low calorie diets (800 cal/day). **Support systems**: counselling and psychotherapy services, patient-led groups, commercial groups, family support, physical activity support services. **Behaviour and lifestyle modification**: self-monitoring and feedback using activity and food diaries or cognitive behaviour therapy for weight loss. **Prescription or OTC drugs**: obesity drugs (orlistat, fenfluramine orsibutramine, fluoxetine, ephedrine and caffeine, phentermine, acarbose), alternative medicines and herbs (protein, vitamins).

		Yes	***No***
Types of education strategies used:	***Nutrition education***	☐	☐
	Physical activity education	☐	☐
	Education on OA	☐	☐

Other (please specify): _____

Please refer to the box below for more information:

Nutrition education: provides basic information on food, cooking methods, eating out, estimating portion sizes. Provision of written materials, educational formats, involvement of family members. **Physical activity education:** teaching strategies and lessons, participation of key stakeholders (parents, teachers, or other educators), knowledge onexercise. **Education on OA:** handouts**,** materials, knowledge on OA and treatment and self-help advice.

Description of intervention in the control group: Usual care, no treatment, waiting list.

12. *Patient education is the process of changing knowledge, attitudes and skills and influencing behaviour to maintain and improve health. It is an active process that involves assisting people in changing behaviour and improving decision-making and coping skills

a.Was patient education explicitly described as an intervention component in the study?

Yes ☐ ***No*** ☐

13. Primary outcome:

Outcome	*Instrument of assessing outcome*	*Timing of outcome assessment*

14. Secondary outcomes:

Outcomes	*Instrument of assessing outcomes*	*Timing of outcome assessment*

15. Adverse events (eg complaints, levels of dissatisfaction, adverse incidents, side effects)

Outcomes	*Instrument of assessing outcomes*	*Timing of outcome assessment*

16. Was patient acceptability of the intervention reported in the study? ***Yes*** ☐ ***No*** ☐

17. Was fidelity of delivery of intervention reported in the study? ***Yes*** ☐ ***No*** ☐

A. Methods used to assess fidelity:

Video-recordings ***Yes*** ☐ ***No*** ☐

Audio-recordings ***Yes*** ☐ ***No*** ☐

Provider self-report checklist ***Yes*** ☐ ***No*** ☐

Patient self-report checklist ***Yes*** ☐ ***No*** ☐

Section B1. Study Characteristics -patients

Study numbers	**Number**
Number of patients originally approached	
Meet inclusion criteria	
Number excluded	
Declined to participate	
Randomised to Intervention groups	
Randomised to Control group	
Dropped out (for each group; with reasons if relevant)	
Lost to follow up	**Intervention group:**
	Control group:

Section B2. Patient characteristics

Demographics	Intervention A	Intervention B	Control group	Total
Age years (mean ± SD)				
Weight (mean ± SD)				
Height (mean ± SD)				
Body Mass Index (mean ± SD)				
Male (%)				
Female (%)				
Treatment Period				
Follow-up Period				

Section C. Quality assessment.

Please see Appendix II for criteria	Yes	No	Unclear
1. Was the randomisation procedure adequate?	☐	☐	☐
Comments:			
2. Were there more than 100 subjects in each treatment group?	☐	☐	☐
Comments:			
3. Was the treatment allocation adequately concealed?	☐	☐	☐
Comments:			
4. Were physicians blinded to the intervention?	☐	☐	☐
Comments:			
5. Were patients blinded to the intervention?	☐	☐	☐
Comments:			
6. Were outcome assessors blinded to the intervention?	☐	☐	☐
Comments:			
7. Was incomplete outcome data adequately assessed?	☐	☐	☐
Comments:			
8. Was intention-to-treat analysis used?	☐	☐	☐
Comments:			
9. Were the treatment and control group similar at baseline?	☐	☐	☐
Comments:			
10. Are all pre-specified outcomes of interest reported in the pre-specified way?	☐	☐	☐

Section D. Level of reporting of implementation fidelity in randomised controlled trials; a recommended data extraction form along with the standard rules and examples of strategies used from Ang et al. (2018)

TREATMENT DESIGN	**Scoring criteria** (++), (+), (Absent but should be present), (N/A)
1. Provide information about treatment dose planned for in the intervention condition	
(a) Length of contact (minutes) (no need to elaborate) (NA if the dose is on an as-needed basis)	
(b) Number of contacts (no need to elaborate) (NA if the dose is on an as-needed basis)	
(c) Content of treatment	
(d) Duration of contact over time	
2. Provide information about treatment dose planned for in the comparison condition	
(a) Length of contact (minutes) (NA if the dose is on an as-needed basis)	
(b) Number of contacts (NA if the dose is on an as-needed basis)	
(c) Content of treatment (+ if only mentions 'usual care'/absence of the intervention implying usual care, without further elaboration of what usual care constitutes)	
(d) Duration of contact over time (NA if the dose is on an as-needed basis)	
(e) Method to ensure that dose is equivalent between conditions (NA if the dose is on an as-needed basis) E.g. Provide similar access and attention to both groups (withholding only the intervention)	
(f) Method to ensure that dose is equivalent for patients within conditions (	

3. Specification of provider credentials that are needed (+ if only the professional discipline is known; ++ If level of experience is known) E.g. Specify professional	

discipline and level of experience, e.g., specialist nurse with more than 10 years of experience in oncology nursing care	
4. Theoretical model upon which the intervention is based is clearly articulated	
(a) The active ingredients are specified and incorporated into the intervention (+ if elaborates on what the essential components of the intervention might be; ++ if explains factors distinguishing it from the comparison condition, i.e., differentiation) E.g. Specify and incorporate essential components of the intervention, and how the intervention differs from the control group	
(b) Use of experts or protocol review group to determine whether the intervention protocol reflects the underlying theoretical model or clinical guidelines (+ if self-derives protocol from reviews or known theoretical models; ++ if uses a panel of experts, protocol review group or advisory committee) E.g. Provide reasons for selecting the intervention evaluated, e.g., reviews or theoretical models, and use experts or protocol review group. Examples used were: cooperative study group, project advisory committee, project advisory group and trial study group	
c) Plan to ensure that the measures reflect the hypothesized theoretical constructs/mechanisms of action1	
5. Potential confounders that limit the ability to make conclusions at the end of the trial are identified (A if confounders identified was that there was no method to ensure the dose equivalence within or between treatment groups; + if baseline demographics measured, or baseline outcome measures measured; ++ if other confounders identified, or if strategies to get around confounders used)	
6. Plan to address possible setbacks in implementation (i.e., backup systems or providers	
7. If more than one intervention is described, all described equally well	
TRAINING PROVIDERS	
1. Description of how providers will be trained (manual of training procedures)	
2. Standardisation of provider training (especially if multiple waves of training are needed for multiple groups of providers)	
3. Assessment of provider skill acquisition	

4. Assessment and monitoring of provider skill maintenance over time	
5. Characteristics being sought in a treatment provider are articulated a priori. Characteristics that should be avoided in a treatment provider are articulated a priori	
6. At the hiring stage, assessment of whether or not there is a good fit between the provider and the intervention (e.g. ensure that providers find the intervention acceptable, credible, and potentially efficacious)	
7. There is a training plan that takes into account trainees' different education and experience and learning styles	
TREATMENT DELIVERY	
1. Method to ensure that the dose of the intervention is delivered as specified	
2. Method to ensure that the content of the intervention is delivered as specified	
3. Mechanism to assess if the provider actually adhered to the intervention plan or in the case of computer delivered interventions, method to assess patients' contact with the information	
4. Assessment of non-specific treatment effects	
5. Use of treatment manual	
6. There is a plan for the assessment of whether or not the active ingredients were delivered	
7. There is a plan for the assessment of whether or not proscribed components were delivered (e.g. components that are unnecessary or unhelpful)	
8. There is a plan for how will contamination between conditions be prevented	
9. There is an a priori specification of treatment fidelity (e.g. providers adhere to delivering >80% of components)	
TREATMENT RECEIPT	
1. There is an assessment of the degree to which patients understood the intervention	
2. There are specification of strategies that will be used to improve patient comprehension of the intervention	

3. The patients' ability to perform the intervention skills will be assessed during the intervention	
4. A strategy will be used to improve subject performance of intervention skills during the intervention period	
5. Multicultural factors considered in the development and delivery of the intervention (e.g. provided in native language; protocol is consistent with the values of the target group)	
TREATMENT ENACTMENT	
1. Patient performance of the intervention skills will be assessed in settings in which the intervention might be applied	
2. A strategy will be used to improve performance of the intervention skills in settings in which the intervention might be applied	

Please refer to the box below for more information:

The 40 items were: whether information about the treatment dose in the intervention and/or control group had been provided; whether there was a method to ensure the dose was equivalent between and/or within treatment groups (intervention and control); whether provider credentials needed were specified; whether the theoretical model upon which the intervention was based was clearly articulated; whether potential confounders that limit the ability to make conclusions at the end of the trial were identified; whether there was a plan to address possible setbacks in implementation; if more than one intervention was described, that all were described equally well; whether there was a description of how the providers would be trained; whether there was standardisation of provider training; whether there was assessment of provider skill acquisition and/or assessment and monitoring of provider skill maintenance over time; whether characteristics sought or avoid in a treatment provider were articulated a priori; whether at the hiring stage, there was assessment of whether or not there was a good fit between the provider and the intervention; whether there was a training plan that took into account trainees' different education and experience and learning styles; whether there was a method to ensure that the dose and/or content of the intervention was delivered as specified; whether there was a mechanism to assess if the provider had adhered to the intervention plan; whether non-specific treatment effects were assessed; whether a treatment manual was used; whether there was a plan for the assessment of whether or not the active ingredients and/or proscribed components were delivered; whether there was a plan for how contamination would be prevented; whether there was an a priori specification of treatment fidelity; whether there was an assessment of the degree to which patients understood the intervention; whether there were specified strategies that would be used to improve patient comprehension of the intervention; whether the patients' ability to perform the intervention skills would be assessed during the intervention period; whether a strategy would be used to improve subject performance of intervention skills during the intervention period; whether multicultural factors had been considered in the development and delivery of the intervention; whether patient performance of the intervention skills would be assessed in settings in which the intervention might be applied; and whether a strategy would be used to improve performance of the intervention skills in settings in which the intervention might be applied.

Section E. Data and results

Pain

Group	Baseline		Endpoint		Change	
	Mean	SD	Mean	SD	Mean	SD

a. Physical function

Group	Baseline		Endpoint		Change	
	Mean	SD	Mean	SD	Mean	SD

b. Quality of life

Group	Baseline		Endpoint		Change	
	Mean	SD	Mean	SD	Mean	SD

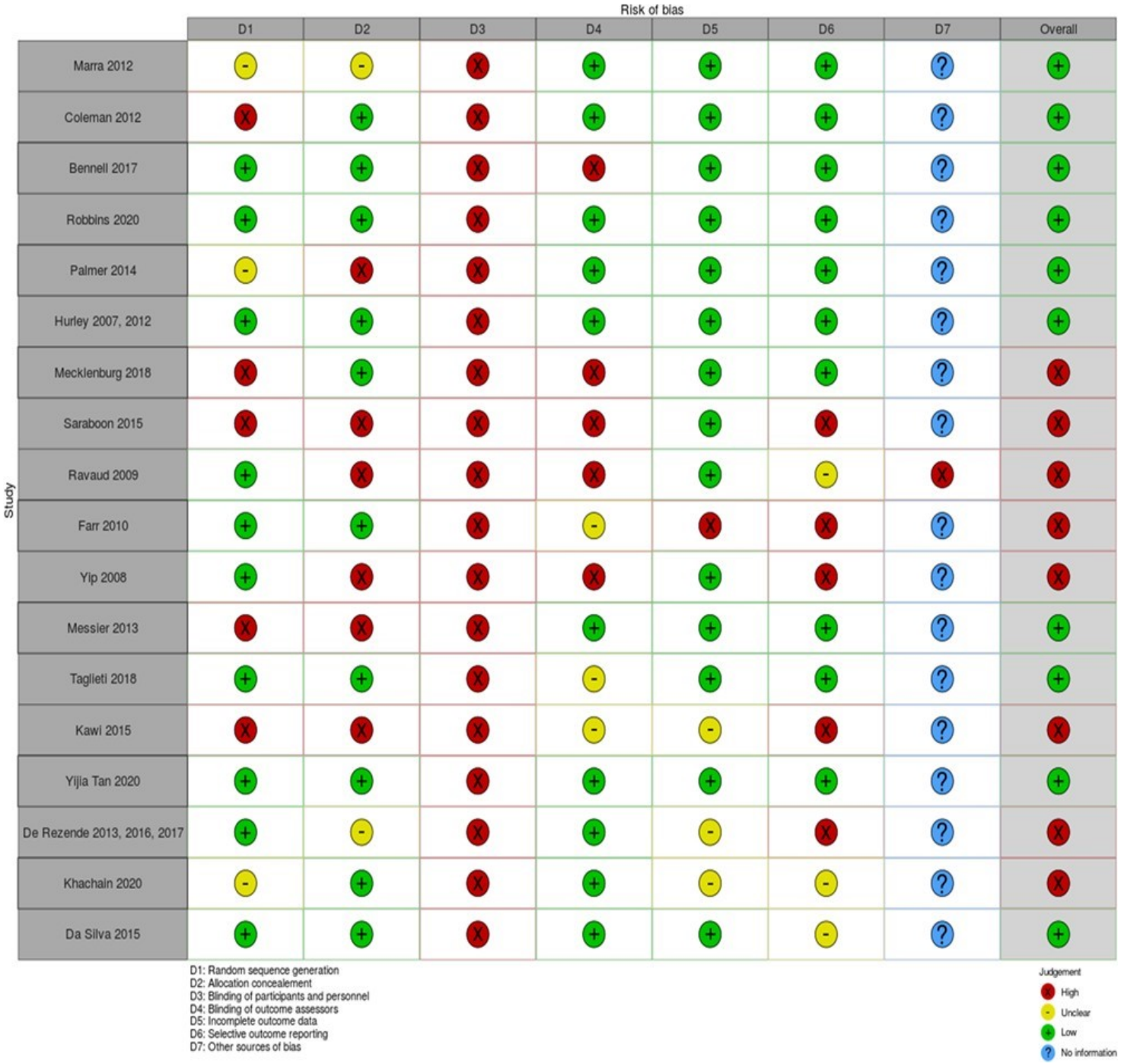
c. Anxiety and Depression

Group	Baseline		Endpoint		Change	
	Mean	SD	Mean	SD	Mean	SD

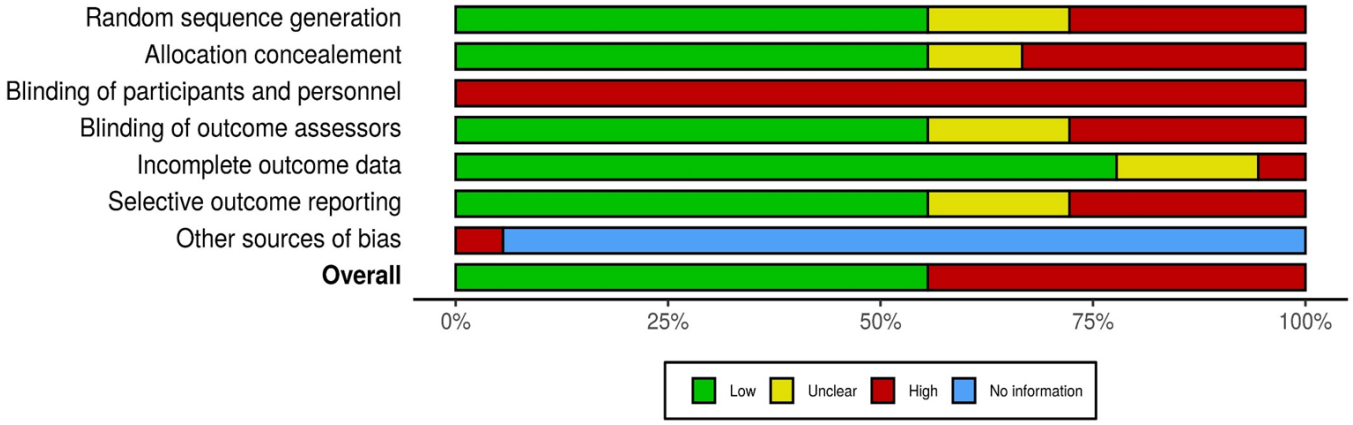
d. Pharmacological data

Group	**Baseline**		**Endpoint**		**Change**
	Medicines		**Medicines**		

Appendix IV Risk of bias summary review



Appendix V Summary plot of the included studies



Appendix VI The semi structured interview guide for the nurse

Nurse's views on experience of delivering the non-pharmacological intervention

We're going to start by discussing your overall views on the knee pain treatment programme, the training you received to deliver it, and then talk about the different components of the intervention separately.

1. Can you tell me what your overall impression of the knee pain treatment programme is, having delivered it for the first time?

Nurse's view of the training received to deliver the non-pharmacological intervention

We are now going to discuss the training you received to deliver this treatment.

2. Can you tell me how you found the training you received
    - Length of training/ number of sessions/ delivery over weeks rather than 2 days condensed
    - Material covered in sessions: too much/too little/about right
    - Opportunities to practice/ feedback
    - Resources/ manual/ electronic material (links to videos)/ links to weight loss resources / exercise sheets/ case-studies

3. How did you find following the manual provided?
    - Probe – reasons for it being easy / difficult to follow.
    - What suggestions do you have to modify the manual to make it easier to use in the future?
    - Any suggestions for improving the training

- How confident did you feel about delivering the treatment once you had completed your training?

Nurse's views on experience of delivering the non-pharmacological intervention

We are now going to discuss how you found delivering the treatment to patients.

4. How did you find delivering this treatment to patients?

- As you know, the treatment package had different components – education on self-managing knee pain, giving the participant exercises, advising them on weight loss, setting individual goals with the participants and assessing patient confidence to achieve goals.
  How did you find delivering these components?
    - [cover ONE at a time]
    - Education
    - Exercise
    - Weight loss
    - Goal setting

- Assessing patient confidence to achieve goals
- Using the diaries (exercise and weight loss)

5. How did you find setting goals with patients?
    - Probe - did they actively participate in the discussions?
6. How did you find the follow-up sessions with participants and providing feedback on participants' progress with their exercises and/or weight loss?
    - Prompts - patient receipt of advice / feedback (any challenges with patients accepting advice or adhering to the treatment given)

- Were there any components that you found challenging to implement?
    - What made it challenging to deliver this component? [cover ONE at a time]
    - Were there any other components that you found challenging to implement? Why.
    - What would help support you in delivering this in the future?

- Were any aspects of the intervention not delivered as planned?
    - What were the barriers to delivering [the aspect]? [cover ONE at a time]
    - What would help support you in delivering this in the future?

We are now going to talk about tailoring the treatment to each patient.

7. How did you find the final session with the participants? Did you feel that they would be able to continue with the advice/exercises/weight loss etc independently?

We'd now like to discuss the resources provided to support you delivery the treatment programme.

8. How useful did you find the other resources during the treatment programme?
    - Probe - handouts / training manuals / thera-bands / exercise sheets/ exercise diaries/ NHS weight loss resource (BMI and weigh loss calculator)/ food diaries/ other weight-loss hand outs
    - What suggestions do you have to improve these resources in the future?

9. Is there any additional support you need in being able to deliver this treatment?

We have come to the end of the interview. Do you have any further comments about the training and/or treatment package that have not been covered?

Appendix VII The semi-structured interview guide for patients

Semi-structured Interview guide for participants.

Experience of treatment for knee pain prior to the study

First of all, I would like to talk about any treatments you may have received for your knee pain before the treatment that the nurse gave you here.

- Can you tell me about what treatments you have previously received for your knee pain, before seeing the nurse?
- How did you find following those treatments?
    - Prompts - easy / difficult.

  Probe why easy / difficult
- How suitable did you find the treatment you received?
    - Please elaborate.
        - Attractive? / met your needs?
- Did you have any concerns about the potential benefits and side-effects of the treatments you received?
    - What benefits / side effects?
    - Length of treatment before the study (painkillers)
    - If yes, what concerns?

Patients' experience of intervention

I would now like to move on to talk about the treatment sessions you received from the nurse and what you thought about them.

Relevance and content

- How useful did you find the sessions with the nurse
    - Probe into what specific advice the patient was given on exercise, weight loss and other adjunctive advice, written advice in booklet and how they found it (usefulness), *one by one*
- What did you find to be most useful whilst receiving treatment from the nurse?
    - Probes – exercise sheets, exercise diary, any other materials
- How useful did you find the exercise sheets?
- Were there any aspects that you did not find useful?
    - Probes – *same as above*
- Was there anything else that you would have liked the nurse to do during the treatment sessions?
    - Probes – gaps in advice, exercise performance (leave more time for patient to answer)

Provider and delivery

- How did you feel receiving this treatment from a nurse compared to a physiotherapist or doctor? (Reference to patients past treatment).
- What did you think about the nurses' ability to communicate about how to manage your knee pain compared to the healthcare professional met before?
    - Prompts - was the advice / information easy to understand / clear / difficult to understand?
    - Follow up on communication
    - Prompts on education / weight loss
    - Probe - examples
- How did you find the pace of the sessions?
    - Prompts –too slow/fast, any awkward moments?

Lifestyle changes and following the advice

I would now like to move onto how you managed to follow the advice given to you by the nurse once the treatment sessions finished.

- How did you find following the advice given by the nurse once you had completed the treatment sessions?
    - Probe – easy/difficult – exercises, weight loss, adjunctive advice
- Can you tell me about what changes you have made to your daily life as a result of taking part in the study?
    - Probe – why changes were made/were not made, ease/difficulty of making these changes
- Have you slowly increased the intensity and frequency of the exercises?
- Have you involved any family members or friends in helping you to manage your knee pain? (social life)

  Probe – what they have helped with, why / why not involved anyone
- Going forward, how do you feel about your ability to manage your knee pain?
    - Now
    - In the long-term.

  Probe – confidence in continuing with exercises / weight loss / using other adjunctive treatments

Changes to perceptions of osteoarthritis and knee pain after the study

- How has your knowledge of osteoarthritis and management of knee pain changed since receiving treatment from the nurse?

  Prompts– *Core treatments* / Was the information too much? / too less to carry home? Could you take it all, remember and carry on?

  Prompt – *add prompts based upon the nurses training booklet and information they tell the patient in the treatment sessions (e.g. importance of paced exercise)*

Overall satisfaction / sequence of treatment

- In general, how satisfied are you with the treatment that you received from the nurse? Is there anything else that can be improved? (*number or words*)
- To what extent do you feel the treatment programme has met your needs?

Is there anything else you would like to say?